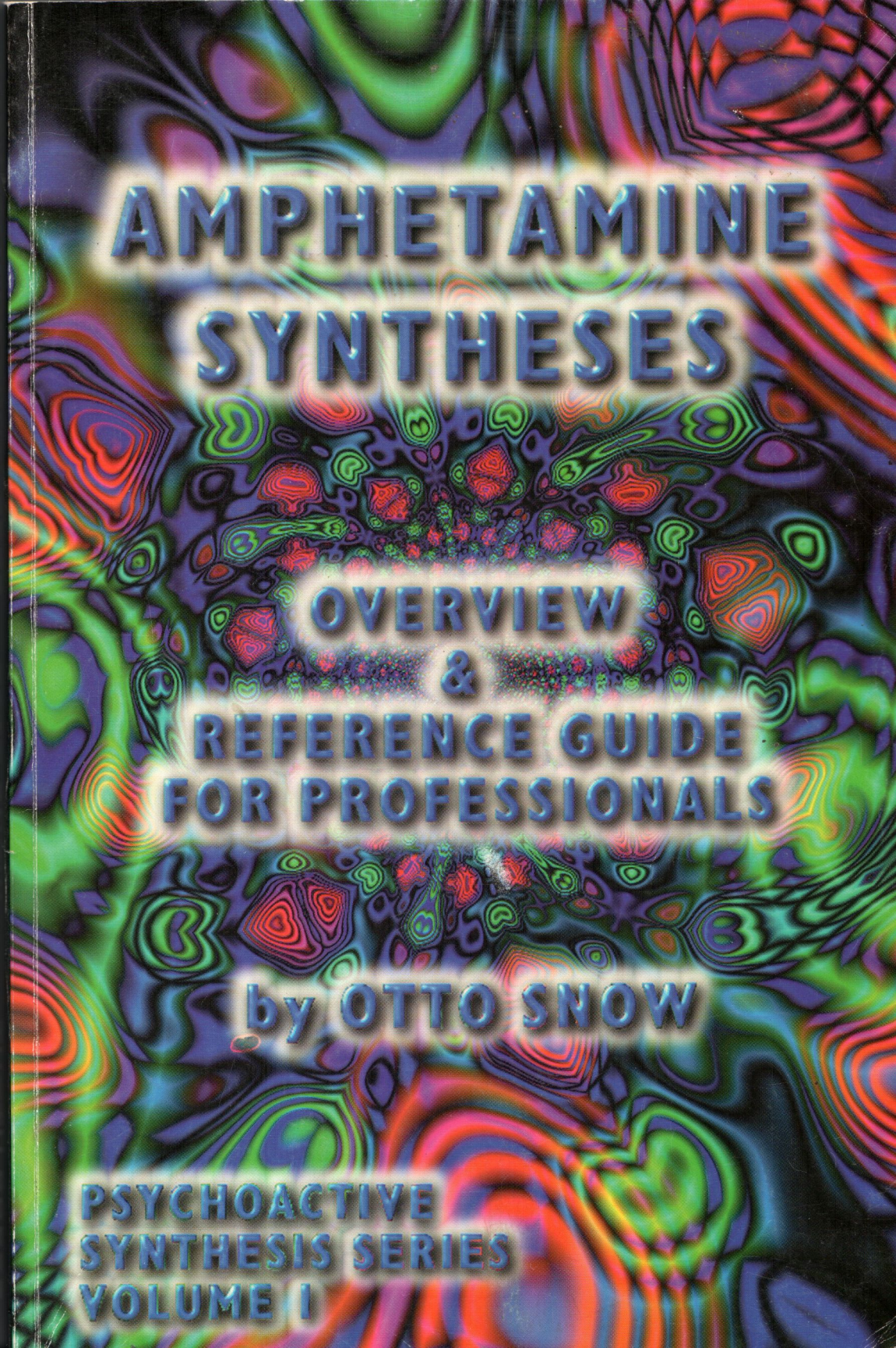

AMPHETAMINE SYNTHESES
OVERVIEW & REFERENCE GUIDE FOR PROFESSIONALS
by OTTO SNOW
PSYCHOACTIVE SYNTHESIS SERIES VOLUME I

AMPHETAMINE SYNTHESES

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&
REFERENCE GUIDE FOR
PROFESSIONALS

by OTTO SNOW

PSYCHOACTIVE
SYNTHESIS SERIES
VOLUME 1

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DEDICATION

I dedicate this book to my father: Harry Snow (1921 - 1994)

I am in appreciation of: L. Lewin, E. Späth, A. Heffter, G. Alles, A. Shulgin, C. Naranjo, T. Sargent, D. Nichols, G. Greer, and all those explorers (too numerous to name) who opened a path into the great unknown, unraveling the mysteries of the brain-mind.

I also want to acknowledge those who unravel the mysteries of the galaxies, stars and beyond, namely Carl Sagan, Copernicus and Galileo.

I want to thank the following: National Institute on Drug Abuse for their publications and help in locating specific toxicological studies; the Drug Enforcement Administration, Office of Intelligence, for their statistics on drug laboratory seizures; Eric Sterling of the Criminal Justice Policy Foundation for directing me to look into the Congressional Hearings prior to the passage of Analogue Act of 1986; Alexander Shulgin for his insight & words of encouragement.

"(If) every public action which is not customary, either is wrong
or, if it is right, is a dangerous precedent.
It follows that nothing should ever be done for the first time."
Cornford 1908

"Nothing will ever be attempted
if all possible objections must be first overcome."
Samuel Johnson (1709-1784)

"Question: ...the rats are saying it (MDMA) seems to be
amphetamine-like but, in fact, it really is not..."
"Obviously no one knows what the rats are thinking..."
Richard A. Glennon 1988

"Recreation is therapy; at least that's what people tell me."
Otto Snow 1992

"Fill the seats of justice with good men,
not so absolute in goodness as to forget what human frailty is."
Sir Thomas Noon Talfourd

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☠ READER'S NOTICE ☠

☞ This reference guide is a tool for the legal profession and should not be misconstrued as a 'cookbook'. Publisher and author take no responsibility for inaccuracies, omissions, or typographical errors. All reactions are generalized. References are included for those seeking greater detail/descriptions on the construction of any specific molecule.

Chemicals and reactions are potentially toxic, explosive & lethal.

☞ This book is for information purposes only. No person is allowed to produce controlled substances without proper permits and authorization. To take/give substances for human consumption whether legal or illegal without a very thorough knowledge of the substance and the health (mental as well as physical) condition/s of the individual is destined to produce catastrophic results and legal ramifications.

Amphetamine Syntheses is a reference guide and overview on the preparation of:

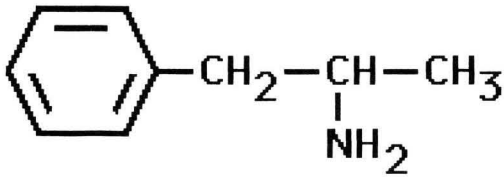
substituted phenylethylamines, substituted amphetamines,
and other active & inactive phenylalkylamines,
neurotransmitters, neurotoxins,
immediate precursors, and precursors
obtained from organic sources.

Series and individual reactions are overviewed and extensively referenced. Many different routes are described on altering the molecular structures of known and unknown neurochemicals. The terms and explanations are simplified and interwoven with historical data. Excerpts from the Congressional Hearing, prior to the passage of the Analogue Act of 1986, are included to give the readers a look at the issues of major concern. Chemicals are indexed for quick reference to assist those investigating suspect laboratories to determine probable cause or reviewing cases to determine culpability, criminal activities or innocence of suspect/s.

This guide is an asset and a necessity for:
lawmakers, attorneys, teachers, counselors,
law enforcement and students alike.

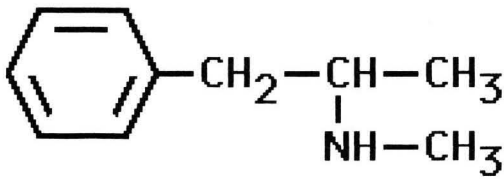
INTRODUCTION

Amphetamine (1-phenyl-2-aminopropane) has long been the focus of study for scientists and organic chemistry students. The uses for amphetamine in the study of brain biochemistry and molecular interactions are endless. To the organic chemistry student it is one of the many psychostimulant drugs that are easily synthesized in the laboratory.



Amphetamine

Although there are numerous molecules which also have psychostimulant effects (Biel 1970), amphetamine has gained the most amount of attention for this effect. The N-methyl (CH_3) homolog of amphetamine (N-Methyl-amphetamine) has also received much attention as it is more powerful than its parent substance.



Methamphetamine

During the 1960's and 1970's it was well known by the 'drug underground' as well as those who studied amphetamines, that speed kills! In 1962, the FDA estimated that 8 billion tablets of amphetamines were being produced legally. Prior to the Controlled Substance Act of 1970 (CSA), over 50 % of all amphetamines which appeared on the streets were being diverted from legal sources. Many physicians were knowingly providing prescriptions for profit.

AMPHETAMINE SYNTHESES

There was a decline in the availability of amphetamines following CSA. The response to the decline in availability of amphetamine did not backlash in the increase of clandestine laboratories producing amphetamines. This was because of the increased availability of cocaine (Burton 1991). Another factor was the increased sales of ephedrine tablets and capsules.

In February of 1980, phenyl-2-propanone was placed on schedule 2. Illicit amphetamine manufacturers were producing P-2-P as an immediate precursor. Over seventy-five percent all P-2-P laboratories used a method employing phenyl acetic acid and acetic anhydride as precursors.

In 1978; 63 seizures of methamphetamine laboratories,
13 seizures of amphetamine laboratories
3 seizures of MDA laboratories.
In 1979; 121 seizures of methamphetamine laboratories
20 seizures of amphetamine laboratories,
5 seizures of MDA laboratories.
In 1980; 121 seizures of methamphetamine laboratories,
23 seizures of amphetamine laboratories,
7 seizures of MDA laboratories.
In 1981; 73 seizures of methamphetamine laboratories,
12 seizures of amphetamine laboratories,
1 seizure of MDA laboratory. (Frank 1983)

There has been a 600% increase in methamphetamine laboratory seizures from 1981 to 1989. In 1981, there were 88 seizures of laboratories; in 1989, there were 652 laboratory seizures reported to be producing methamphetamine (Irvine 1991).

80% of all drug laboratory seizures were producing methamphetamine. In 1989, fifty-three percent of the laboratories were using a method employing ephedrine, red phosphorus and hydrogen iodide to make d-methamphetamine. Forty-seven percent of the laboratories were producing d,l-methamphetamine from P-2-P. In 1990, ninety percent of methamphetamine laboratories in California were using the ephedrine reduction method to produce methamphetamine (Heischober 1991).

AMPHETAMINE SYNTHESES

The most commonly used synthesis for amphetamine and methamphetamine uses P-2-P in combination with aluminum amalgam and methylamine (Frank 1983). The Leuckart method is the most popular method used in Norway and the Netherlands (Soine 1989).

In 1988, 50% of methamphetamine laboratories seizures occurred in California, followed by thirteen percent in both Texas and Washington (Irvine 1991) states.

We must take into account that in all seizure statistics, these numbers do not include margins of error or any statistics of non-illegal laboratories that were destroyed and individuals terrorized by law enforcement. It is paramount in any drug case and in any democracy that the up holders of the law have to follow the same laws that everyone else is expected to follow. A knowledge of drug chemistry is necessary so that law enforcement can protect themselves from toxic chemicals used in drug synthesis. Training in these areas is grossly lacking. Compensation and restitution to those individuals who are inadvertently terrorized in the war on drugs must be addressed as it is long over due.

A freebase form of d-methamphetamine called 'ice' appeared in California. The drug was being imported by organized crime into the US from countries along the Pacific rim (Korea, Taiwan, Philippines) and the distributed in the US by organized crime groups.

"Smoking gives a rapid onset of effect of the drug, comparable in many ways to that from intravenous (IV) administration. The rapid reinforcement also enhances the addicting power of the drug."
(Cook 1991)

Drugs such as MDMA and methamphetamine will remain popular drugs because their large scale synthesis does not involve a knowledge of sophisticated chemical procedures. Chemical suppliers can request End of Use statements from those purchasing suspect chemicals as a deterrent.

Most chemicals used in the synthesis of drugs can be purchased anywhere as they have many uses and are articles of commerce.

The forensic chemist can look for the trace impurities that occur in a drug sample and determine how the drug was manufactured. Dope chemists manufacture crude drugs which are active, but contain isomers, impurities of incomplete synthesis, etc. Factional distillation of immediate precursors and end products is generally not done leaving 'finger prints' for those who investigate drug samples and drug laboratories.

The book is written for all those who are studying or investigating the syntheses of amphetamine, phenylethylamine and chemical analogs (eg. homologs, and congeners). I would recommend that all readers read PIHKAL for a look into the experiences of a modern explorer. Readers should also read an article written by Dal Cason (1990) for an overview on the syntheses of MDMA.

"During clandestine laboratory investigation the forensic chemist may be asked to illustrate the synthetic route used by the defendant(s). For this reason, the forensic chemist should have a clear understanding of the synthetic routes available to the clandestine chemist." (Cooper 1984)

To date, I have found no book that describes the synthesis of these molecules in a way in which lawyers, judges, law enforcement and students can easily comprehend. Reaction overviews, precursors, and various molecules are indexed and referenced for easy location of information.

Years ago, chemistry didn't have the impact that it does today. We are all affected by new drug development. The role of the authorities as upholders of justice necessitate a basic understanding of neurochemistry. Although we can have professionals who are more then willing to interpret the law and the science for us; we all must gain a better understanding of drug chemistry to protect our rights and the rights of future generations.

Mr. James N. Hall: "The name "Designer Drugs," caught the attention of media over the past year and a half as a new trend in America's illicit drug scene. As you are aware the term does not refer to a particular pharmaceutical classification but rather to a method of making new products for the illicit market." (5/1/86).

The primary objective of drug laws is to stop dangerous drugs from being sold or distributed (dumped on the masses for consumption); yet the Analogue Act does not clarify this problem.

The Analogue Act fails to differentiate between a scientist working on a molecular series and a drug chemist distributing dangerous drugs on the street. The law inadvertently attacks the method of science.

There are many arguments to the Analogue Act which provide a wealth of debate for those who would like to see science move out of the courtroom and back into the laboratory where it belongs. (US vs. Forbes) (Shulgin 1986; 1991) & numerous others.

Science and research are the front lines in war against disease. Pick up a copy of the Physician's Guide to Rare Diseases. Suffering and death don't wait for major pharmaceutical monopoly interests to develop drugs. Pain and agony don't wait for big business and Congress to get around to listen to their screams. Injustice and victims of suffering and disease don't wait for laws to allow them to research, develop and take substances to help themselves (this is our right to life).

The Chemist

There are millions of chemists in the United States, yet very few create drugs for distribution. Most chemists are interested in an aspect of molecule that they want to study further. In areas where there are high concentrations of chemical plants or industry there will also be larger concentrations of chemists synthesizing all sorts of molecules for study. Law enforcement in these industrial areas target those who distribute drugs.

Of course without drug laws (Harrison Drug Act 1914), the food supply would be 'spiked' with narcotics.

American science and technology is very aggressive, sometimes unorthodox, inventive and revolutionary. Research is an adventure, a mystery to be solved; a path to blaze into the unknown; to advance knowledge which in turn our evolutionary society benefits from. The sciences and advanced technologies have always attracted those who are not satisfied with the mundane and question conventional wisdom. There has always been simultaneous attacks against/respect for those who are willing to investigate the unknown in hopes of bringing back something that will change the world; the eureka!

President Kennedy's setting of long term goals for the nation (race to the moon) was a national effort towards a common goal. Industries rose as the exploration of space was promoted. Model rocketry spurted hands on experience, reinforcements; an affirmation that all Americans could take part in the national goal. Those technologies that developed were then applied to civilian applications.

Decade of the Brain (Public Law No. 101-58) has appeared to be much different than a national effort in which everyone can take part in. Independent chemists are not publishing their research because of repressive laws and atmosphere. Massive quantities of data have been generated from those who qualify for government grants, but diseases and drug addiction still ravage the nation because of inadequate drug development. Tests to determine defects in neurotransmitter systems have been discovered, yet are not being made available to patients. Complacency in the medical profession allows poor quality medical care. The total disregard of patients' rights and no national health care coverage for the American people is a result of Congress representing medical/pharmaceutical/insurance PACS instead of the American people.

Currently the development of safer drugs and better drugs is occurring at a snail's pace. The development of new medications faces more hurdles in getting drug approval guarantees that only very large corporations can afford the endeavor (pharmaceutical feudalism).

50 Million Americans are effected by mental disease. "Depression afflicts 5.4 million people. Manic-depressive disorder, a different condition altogether, affects about 900,000. Among anxiety disorders, 14 million people suffer from phobias, 1.8 million from panic disorder, and 2.7 million from obsessive-compulsive disorder." (Stinson 1990).

Many chemists produce psychopharmaceuticals for their own studies. The Analogue Law has produced an atmosphere of fear that hampers the communication and publication of discoveries. The analogue law is so vague and misleading that it has hampered research, scientific inquiry and progress in the neurosciences. Laws that are passed with good intentions must be followed up with amendments to modify short falls which become apparent later.

Prior to the analogue law, chemists through out the nation were generating new molecules for study. The neurosciences were emerging (and still are) as a new frontier of research. Simultaneously many

individuals did not publish in the scientific journals do to prior illegalization of any molecule which may have usefulness in the treatment of the ill. The mediocrity has long made front page news of an issue that can be used as a new sacrifice to feed on like carrion or when politicians need a whipping post to point at as the cause of social problems and unrest.

The object of the analogue law was to stop drug chemists who slightly altered the structure of schedule 1 substances to produce the same effect of the scheduled substance while getting around the law. This is true for some dope chemists who maybe trying to 'get around the law', but dope chemists are not interested in the law, that is why they are criminals.

The neurochemist is not intending to get around the law, the neurochemist is interested in neurochemistry and doing good science. This may also include the testing of a molecule in human subjects to determine its activity or non-activity; to determine what a molecule does or does not do. Applying animal studies to speculate on the activity in humans without testing the molecule on humans remains windmills in the mind of Don Quixote.

The analogue act fails to discriminate the difference between research activities (including self exploration, whether amateur or professional) and the activities of criminals.

The organic chemist that is studying neurochemistry will have hundreds if not thousands of journal articles on a diversified family of psychoactives and neuro-molecules, their synthesis; effects in laboratory animals and human subjects. Dope chemists will generally have notes on the specific synthesis of an illegal substance.

Science is a method. Observation, hypothesize, development of a experiment which will prove or disprove (shed light on what you are looking into) hypothesis, formulation of theory. Continue...

If anything that the analogue law has done is an attack on the method of the development used in the neurosciences. It is safer that a chemist take a molecule themselves than to test (dump) a crude molecule nationally.

The neurochemist has the bug for exploration vs. the hardened dope manufacturer who has a bend towards criminal activities (eg. stealing, violent crime). There is a substantial difference between a chemist having a hobby set up synthesizing small quantities of neurochemicals and the evil hardened 'crank lab' mentality so dramatized by the media.

The dope criminal will dumb large quantities of toxic waste in vacant lots, rivers, poisoning the ground and water or throughout the city sewage system. This can be very dangerous and can blow up an entire neighborhood. Explosions ripping up city blocks have occurred with gasoline vapors escaping from old storage tanks.

If the career criminal were not cooking up some crude drug product (flask gunk) to dump on a city, this person would be doing some other sort of violent felonious act. He or she might be robbing your home or local grocery store, hooking healthy children with addictive drugs; forcing them into the sex trade to sell their bodies for dope that the pusher sells them. Satan lurking in the shadows of the school yard feeding innocent children rat poison.

The neurochemist may produce a small quantity of a neurochemical and share this with close associates for study further. All explorations involve a degree of risk. Yet the Analogue Act makes no difference between the activities of the explorer/scientist and actual criminal activities committed by evil individuals.

At the time that Mr. Rangel introduced H.R. 2014 (April 4, 1985) the bill was primarily designed "to eliminate the manufacture and distribution of illegal synthetic narcotic analogs." When H.R. 2977 was introduced by Mr. Lungren, 'designer drugs' were identified as to "include, but are not limited to, the following: phenylethylamines, N-substituted piperidines, morphinans, ecgonines, quinazolinones, substituted indoles, and arylcycloalkylamines." (July 11, 1985). Passed S.1437. (Dec, 18, 1985).

Phenylethylamines are the building blocks of molecules used in the study of endogenous catecholamines, their isomers and analogs (eg. adrenaline, noradrenaline). The indole family of molecules compose of the serotonergic neurotransmitter system of isomers and analogs (the tryptamine family of endogenous neurochemicals).

Lawrence Smith: "I don't care which proposal we approve, but I want to see a designer bill enacted into law this session." 6/1/86

In hindsight we can see that although the law was intended to curtail the activities of a potential drug menace (narcotics) in the short time, it did not stop illicit drug laboratories in this nation. Dangerous drugs continue to be produced by those who are criminals. While those

who want to study neurochemistry are placed in the quagmire of having to defend their inquisitiveness.

Until these short falls are ironed out, it would appear that patenting a molecule, IND, NDA etc. prior to testing, seems like 'the cart before the horse.' Scientists are not going to patent every chemical, or to do rigorous testing on any one specific structure (eg. especially when reviewing several series of structures), with the scrutiny or lack of done for FDA approval. Their objective is scientific inquiry. Those who are ill are not going to be able to develop and go through the FDA approval process for a substance that helps/or might help them, they are already fighting for their lives.

"For the most part, however, if the people who you have annoyed are part of the government, their actions against you will be motivated less by beliefs or philosophies which run counter to your own, than by the simple desire to remind you that they have far more power than you do, and that, even if you don't fear that power, you should at least have a healthy respect for it." (Shulgin 1997 in TIHKAL)

Einstein : "(there is) a duty in refusing to cooperate in any undertaking that violates the Constitutional rights of the individual. This holds in particular for inquisitions that are concerned with the private life and the political affiliations of the citizens..."

Senator Joseph R. McCarthy (Committee for UnAmerican Activities) called Einstein an enemy of America for this statement.

CHAPTER ONE: PSYCHOPHARMACEUTICAL TRADE

In 1914 the Harrison Drug Act was passed by Congress to stop the adulteration of over the counter medicinals and food products with narcotics. This act placed the responsibility of narcotic distribution in the hands of the pharmaceutical-medical community.

The face of mass addiction has changed but the name of game remains the same. All drugs are accommodated by the biochemistry of the body and or brain (Gaday 1965). The degree of accommodation could be viewed as a dependence scale. The screening of a drug's dependence potential in laboratory animals is called reinforcement testing. Some drugs produce more habituation and or addiction (reinforcement) than others. Some drugs produce habituation-addiction more rapidly than others. The primary ability to produce addiction depends on how the molecule interferes and interacts with an individual's normal biochemistry.

All psychotropic-psychoactive drugs produce biochemical changes in brain chemistry (neurochemistry) (Maas 1977) (Meadows 1982). All psychotropic (psychiatric) drugs produce withdrawal (Gardos 1978). The types of withdrawal symptoms depend on the drug's actions in the body and the body's and brain's biochemical adjustment to non-drug biochemistry. The severity of the withdrawal symptoms increases with the length of time that a person has been taking the drug. All drugs which have been taken chronically will produce withdrawal.

Some drugs (e.g. benzodiazepines) have been reported to produce withdrawal symptoms that can last for a year after discontinuation of the medication (Higgitt 1985). Benzodiazepines are reinforcement drugs, this class of drugs is addictive. Benzodiazepine tranquilizers can produce addiction in individuals in a short a period as four weeks. Most individuals who become addicted to benzodiazepines will remain addicted for the rest of their lives.

The withdrawal symptoms of most psychotropic (psychiatric) drugs resemble the same condition-symptoms that the drug is approved (by FDA) to treat.

Barbituric acid was first synthesized by A. Bayer in 1863. Substituted barbiturates were first synthesized by Conrad and Gutzeit in 1882. In 1904 barbituric acid was first used as a sedative. In 1936, three hundred suicides were reported to have taken place with the use of barbiturates (Hambourger 1939). In the same year approximately 80 thousand kilos (80 metric tons) of barbiturates were dispensed in America for drug use. 2 Million doses of barbiturates were being consumed daily.

Amphetamine was first synthesized in 1877. By the 1930's, amphetamines were being dispensed by medical practitioners for use as nasal decongestants, mood elevators, in the treatment of exhaustion, narcolepsy and as psychostimulants. In 1943 the Air Force outlined the use of amphetamine for pilots and ground troops to avoid sleepiness. It was also noted that adequate rest must follow each period of exertion (Air Force 1944). During this time practitioners were dispensing amphetamine as the new panacea for everything that ailed the human condition.

In the 1930's an insecticide called phenothiazine was used in agriculture. It was also used as a urinary antiseptic and as a treatment for pin worm infestation. During the 1950's it was discovered that analogs of phenothiazine possessed powerful sedative effects. This effect was exploited; phenothiazines were then used on mental patients.

Asylums were closed down as sedated mental patients were sent home or into the streets. Elderly individuals in nursing homes were drugged to produce less work for attendants and medical staff.

Once heralded as the 'new miracle drugs;' today the phenothiazines are considered no less then chemical straight jackets (Beers 1988; Garrard 1991; Sloane 1991). Analogs of the phenothiazine class of drugs continued to be patented, manufactured, and dispensed to mental patients, the elderly and the public. Phenothiazines and analogs are a class of drugs known as antipsychotics, major tranquilizers and neuroleptics. Their action is not a cure for mental illness or old age, but to shut down the limbic system of the patient. The limbic system is a part of the brain that controls decision making, reasoning, reality, personality; those behaviors and emotions critical for survival and self preservation.

A class of antidepressants was accidentally discovered in the 1950's. These drugs inhibit enzymes (monoamine oxidase) which break down neurotransmitters. Their abbreviation is MAOI.

Pharmaceutical firms patent new drug analogs to:

1) reduce the toxic effects (referred to as side effects, adverse effects).
2) alter the activity of a previous drug of the same class.
3) get around a competitor's previously patented drug.
4) get a monopoly on the distribution of a new drug.
5) make a major profit; big business.

During the 1960's another class of drugs called the benzodiazepines began being marketed as tranquilizers and sleep aids. They were touted as being safe, effective and non-addictive. Pharmaceutical firms began designing, patenting and marketing numerous analogs of benzodiazepine drugs. According to government statistics, in 1981, pharmacies dispensed 65 million prescriptions of benzodiazepine drugs. In 1985, retail pharmacies dispensed 81 million prescriptions of benzodiazepine drugs (61 million prescriptions for tranquilizers and 20 million prescriptions for sedative-hypnotics). In 1987, pharmacies dispensed more than 85 million prescriptions for benzodiazepine drugs (NADI). These statistics do not include the millions of free samples given by practitioners.

During the 1960's another class of drugs was created, patented and dispensed by pharmaceutical firms; they are known as iminodibenzyl drugs, commonly referred to as tricyclic antidepressants. Their actions are like that of cocaine and amphetamine (Scheel-Krüger 1972) (Pacholczyl 1991). Amitriptyline, and nortriptyline, both have a high affinity to d-LSD binding sights in the brain and reduce serotonin activity (Ogren 1979). Imipramine, desipramine, chlorimipramine and mianserine reduce d-LSD binding in the brains of rats (Ogren 1979).

Psychiatric drugs, known as psychotropic drugs, neither cure disease, rebuild the body or mind and can actually create disease (A Killing Cure, Confessions of a Medical Heretic, Dr. Caligari's Psychiatric Drugs, Drug Interactions in Psychiatry, The Neuroleptic Malignant Syndrome and Related Conditions, Neuropsychiatric Side-Effects of Drugs in the Elderly, Psychiatric Drugs, Hazards to the Brain, Toxic Psychiatry, You Must Be Dreaming).

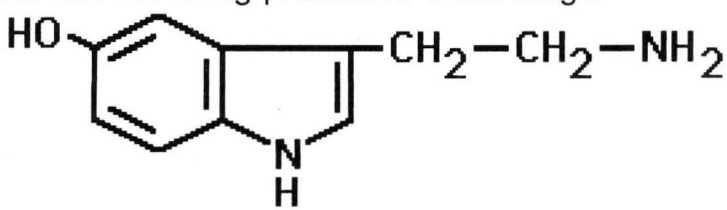
Neuroleptics cause tardive dyskinesia, drug induced parkinsonism and increase the severity of schizophrenic symptoms in patients who stop taking them. They also produce ocular, liver, and cardiac damage. Although these drugs are classified as antipsychotics they induce hallucinations, severe depression, confusion, and memory problems in many patients. Anticholinergic syndrome, neuroleptic malignant syndrome and serotonin syndrome (Sternbach 1991) are toxic psychotic reactions produced by these drugs. All syndromes can cripple or kill the patient by paralytic ileus and cardiac arrest.

The benzodiazepines have been determined by the government and scientific studies to only be affective sleep aids for 14 days.

Benzodiazepines reduce sleep stages 3 and 4. Both sleep states are necessary for the proper functioning of the brain (Willis) (Hecht).

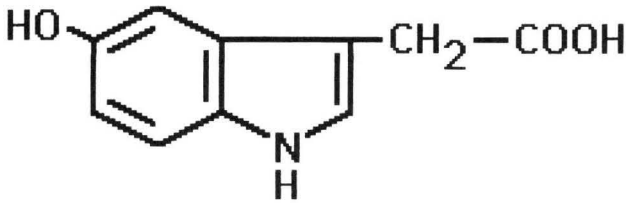
Tricyclic antidepressants have been dispensed as a panacea to patients for any symptoms which in one way or another may qualify under the symptoms of depression. These drugs produce severe dryness of mucous membranes leading to respiratory infections, ocular problems and disease, constipation, candidia infections, mood-swings, memory problems, sleep problems (insomnia, reduction of REM sleep) and a long list of miscellaneous symptoms.

In recent years there has been more public awareness to the increasing statistics of suicides and violence occurring in individuals who are being prescribed these drugs.



Serotonin (5-Hydroxy-tryptamine)
(Neurotransmitter)

Tricyclic antidepressants (amitriptyline, nortriptyline, mianserine) do not increase serotonin (a neurotransmitter) neurotransmission in the brains of patients (Aghajanian 1978) (Murphy 1978)(Coppen 1976)(see also Sussaman 1995). These drugs block both presynatic and post synaptic receptors (Ogren 1979). Drugs such as zimelidine primarily act by blocking presynaptic receptors, but also block post synaptic receptors and reduce serotonin neuron firing with chronic use. Tricyclic antidepressants (amitriptyline and nortriptyline) also decrease a serotonin metabolite in the spinal fluid called 5-hydroxy indole acetic acid (Maas 1977).

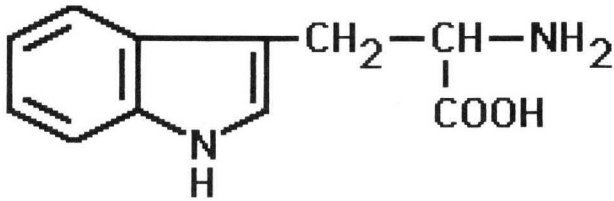


5-Hydroxy-indole-acetic acid (Serotonin Metabolite)

Reduced levels of this biochemical marker have been found in suicide victims (Biology of Suicide). A reduction of serotonin levels also reduces levels of 5-HIAA. Laboratory animals have been fed diets missing L-tryptophan to cause serotonin depletion. The depletion of serotonin resulted in sleep loss, aggression and violence in the laboratory animals (Brown 1986) (Messing, 1976, 1978) and depression in humans (Beitman 1982) (Coppen 1976). Pretreatment of laboratory animals with 5-hydroxy-tryptophan (Pradhan 1978) (Taylor 1977) blocks the stimulation induced by cocaine.

An essential amino acid called L-tryptophan is necessary in our diets for the production of serotonin in our body and brain. L-Tryptophan is absorbed from the food we consume. L-Tryptophan is bound to other proteins in our food. Some individuals can not absorb proteins such as L-tryptophan unless they are bound to dipeptides (Fleischmajor 1961).

L-Tryptophan increases both serotonin in the brain and 5-hydroxy-indole acetic acid in the spinal fluid.



L-Tryptophan
(Essential Amino Acid) (Serotonin Precursor)

All drugs are potentially dangerous. Whether obtained over the counter (OTC), by prescription or from the street does not change the deadly potential of drugs.

Psychotropic (psychiatric) drugs are generally prescribed for short periods, to insure that the patient is closely monitored for therapeutic effect, toxic effects and behavioral disturbances. In all long term drug treatment there must be medication management and communication with psychotherapist.

Psychotherapy is done concurrently by someone independent of the prescribing physician; a patient may then be evaluated to determine therapeutic usefulness of a psychotropic medication.

When drugs are dispensed with no regard for the safety, health and welfare of the individual and no psychotherapy is done, then, the risk out ways the benefit; hence the drugs become toxic, life threatening and deadly.

CHAPTER 2:
THE HISTORY OF PSYCHOACTIVE CHEMISTRY

Louis Lewin used the term phantastic (meaning drugs of illusion) to describe the class of drugs which have the effects of mescaline. This class of drugs has been referred to as hallucinogens (drugs which produce delusions), psychotomimetics (means induces psychosis), psychedelics (mind-manifesting) and numerous new terms to describe/clarify the specific effects of these phantastic drugs.

Most scientists working on these types of materials describe them in more defined/refined terms. The term entheogen (awakens the God within) is used to describe the actions drugs or botanicals which have been extensively used as religious sacraments and provoke religious enlightenment. These drugs include mescaline, LSD-25 and psilocybin.

The term stimulant is used to describe psychostimulant drugs such as cocaine, amphetamine, methamphetamine, and to a lesser extent ephedrine and phenylpropanolamine. Tricyclic drugs such as amitriptyline and imipramine also cause stimulation in some individuals and sedation in others. All psychostimulant drugs will produce hallucinations if taken in large dosages or for extended periods of time. Amphetamine psychosis produces symptoms which closely resemble schizophrenia (Giffith 1970) (Jönsson 1970).

The substituted amphetamines have many different effects, high doses generally will produce visual activity, where as low dosages produce mood elevation. Most studies (human testing) done on these molecules involved administering large doses to patients, which would naturally produce effects outside therapeutic window and increase adverse effects. The dosages, listed for the molecules described, are the tested dosages noted in the literature and should not be misconstrued as an excepted or 'safe' dosage within any therapeutic window.

3,4,5-Trimethoxyamphetamine (TMA) is hallucinogenic; so is 4-methyl-2,5-dimethoxyamphetamine (DOM). Yet there are also differences between the effects of both of these drugs. DOM has been reported to produce more physical awareness (concern for physical health) in subjects and is longer acting then other amphetamine psychoactives (14-20 hours).

MDMA (3,4-methylenedioxy-N-methylamphetamine), and MDEA (3,4-methylenedioxy-N-ethylamphetamine) are termed empathogens. These substances produce feelings of empathy and bonding in subjects. These drugs are not considered hallucinogenic at therapeutic dosages. MDMA's effects are shorter acting than that of MDA. The 3,4-methylenedioxy class of drugs is unique in its effects, differing from both hallucinogens and stimulants.

Another class of phenylalkylamines has been found to be non-hallucinogenic and may have psychotherapeutic usefulness. One member of this family of molecules called N-methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine has been tested in humans (Nichols 1986). This family of molecules is called entactogens.

Hofmann's synthesis of LSD-25 and subsequent discovery of its effects in 1943 catalyzed research and studies in neurochemistry and the neurosciences. Before Hofmann's serendipity, the primary psychotomimetic of study was mescaline.

Mescaline's effects were known throughout the world during the first half of the 20th century. It was used in the scientific community, the medical community and by those who wanted to know more about the brain-mind sciences. Aldous Huxley took 400 mg. of mescaline and opened the world to the novel The Doors of Perception.

Many psychoactive substances appear in Schedule 1 meaning:

1) The drug or other substance has a high potential for abuse.

2) The drug or other substance has no currently accepted medical use in treatment in the United States.

3) There is a lack of accepted safety for use of the drug or other substance under medical supervision.

Some substances which have little potential for abuse are still included in Schedule 1. A botanical called *Tabernanthe iboga* appears in Schedule 1. Its effects resemble *Datura*, which is a deliriant, and is not considered 'user friendly.' N,N-dimethyltryptamine (DMT), a neurotransmitter in the brain, is excreted in the urine of all individuals and is a controlled substance.

According to the Federal Code of Regulations the following phenylalkylamine chemicals, their isomers (optical, geometric, positional) and their salts are currently listed under Schedule 1 as hallucinogenic substances:

4-Bromo-2,5-dimethoxyamphetamine
4-Bromo-2,5-dimethoxyphenylethylamine
2,5-Dimethoxyamphetamine
4-Methoxyamphetamine
5-methoxy-3,4-methylenedioxyamphetamine
4-methyl-2,5-dimethoxyamphetamine
3,4-methylenedioxyamphetamine
3,4,5-trimethoxyamphetamine
3,4,5-trimethoxyphenylethylamine
3,4-methylenedioxy-N-methylamphetamine
3,4-methylenedioxy-N-ethylamphetamine
3,4-methylenedioxy-N-hydroxyamphetamine

With every new discovery in science there is a new innovation, and with it was a new way of looking at the world; a new paradigm. The 1950's and 1960's were the dawn of the techno-revolution, a revolution in art, in forms of media, expression and concern for the rights of individuals and the environment. The world turned on, scientifically, technologically, intellectually and spiritually.

During the 1960's and 1970's, many new psychoactives were synthesized and studied. These materials primarily remained in the hands of scientists, psychologists and chemists. Only sporadically would these psychoactives appear on the street, until the 1980's.

In the 1980's, the DEA placed ads in Popular Science for formulas on preparing controlled substances and also placed ads offering precursors and immediate precursors used in these formulas (NY Times, 1983). Chemists through out the country began ordering and selling precursors and immediate precursors. These precursors and immediate precursors were used by chemists to construct new uncontrolled psychoactives for research and psychotherapy. One of the many psychotherapeutic drugs which appeared on the street was MDMA, then MDEA and 2CB.

Dr. Greer states: "The single best use of MDMA is to facilitate more direct communication between people involved in a significant emotional relationship. Not only is communication enhanced during the session, but afterward as well. Once a therapeutically motivated person has experienced the lack of true risk involved in direct and open communication, it can be practiced with out the assistance of MDMA."

The media publicized the use of MDMA as an adjunct with psychotherapy to save failing marriages, relationships and families. A DEA spokesperson, Frank Sapienza, said to Chemical & Engineering News (10/9/85):

"I think the different views of MDMA are compatible. They might not call that abuse. They might call it recreational use. Must go through accepted procedures to prove that it is safe, that can be produced in pure form, and it treats some condition. MDMA may be able to fit into that category, but the studies have not been done to show that. Therefore, we have to say that it has no accepted medical use, and it has to go into Schedule 1."

The National Institute on Drug Abuse stated that MDMA is a nationwide problem and serious health risk. They further stated the adverse effects are much like amphetamines and cocaine. They cited, psychological difficulties, including confusion, depression, sleep problems, drug craving, severe anxiety and paranoia.

These adverse symptoms are commonplace reactions of psychotropic drugs such as amitriptyline, promethazine, flurazepam, diazepam and thioridazine. Most psychotropic drugs are not controlled.

The DEA's stand on MDMA was that it was neurotoxic to serotonergic neurons. The neurotoxic effect of amphetamine and fenfluramine towards serotonergic neurons has been demonstrated and known in the scientific community for two decades. Both amphetamine and fenfluramine can cause increased aggression and violence in individuals who are prescribed these drugs. Fenfluramine has been taken off the market (FDA) because it causes heart disease.

Amphetamine is listed under Schedule 2 meaning:
1) The drug or other substance has a high potential for abuse.
2) The drug or other substance has a currently accepted medical use in treatment in the United States or a currently accepted medical use with severe restrictions.
3) Abuse of the drug or other substance may lead to severe psychological or physical dependence.

Schedule 2 also includes P-2-P which is one of many immediate precursors to amphetamine and methamphetamine.
P-2-P also appears under the chemical names benzylmethylketone or phenyl-2-propanone.

Fenfluramine is listed under Schedule 4 which means:
1) The drug or substance has a low potential for abuse relative to the drug or other substances in Schedule 3.
2) The drug or other substance has a currently accepted medical use in treatment in the United States.
3) Abuse of the drug or other substance may lead to limited physical dependence or psychological dependence relative to the drugs or other substances in Schedule 3.

Mr. Sapienza (DEA) also stated that MDMA's abuse potential was demonstrated by the fact that a lot of the drug is being synthesized and sold on the street.

It is a known fact that many people use drugs in personal psychotherapy. Many individuals are seeking alternative forms of psychotherapy and adjuncts to psychotherapy because of the short falls of conventional psychotropic drugs:

1) psychotropic drugs do not cure mental and emotional afflictions.

2) the toxic effects of psychotropic drugs make them ineffective for many people to tolerate.

3) the addictive nature of many psychotropic drugs. Drug addiction effects the lives of all those around them.

4) psychotropics can mimic mental illness, especially on withdrawal. Drugs should be discontinued with the assistance of those who have a very thorough understanding of drug mechanisms and patient biochemistry. Rapid discontinuing of some medications can cause serious reactions. Some drugs must be tapered.

5) chronic drug treatment is not a solution for mental or emotional afflictions. Psychotherapy is necessary to gain coping skills.

6) the high cost of psychotropic drugs. Price gouging is no good.

7) psychotropics can cause violence & rage reactions in some patients.

8) conventional psychotropic medications are not effective in all biochemical disorders (eg. the use of marijuana to help PTSD victims).

9) there are few, if any, protections for patients who are abused by psychiatry in the United States. It is important that patients find psychiatrists who have a strong understanding of brain biochemistry and drug interactions. There are many very knowledgeable psychiatrists in this country. Patients must be treated with compassion, understanding and empathy or psychiatry becomes a pill mill. This country needs more research and faster drug development.

Psychiatric drugs will remain the arsenal against what afflicts the human condition until; a better understanding of disease mechanisms is achieved; until governments, states, agencies, associations, institutions and communities recognize the needs of and protect the rights of the individual and families.

Many psychologists and psychotherapists were caught off guard with the DEA's emergency scheduling of MDMA under Schedule 1 in July 1985. Psychotherapists requested that MDMA should be placed on Schedule 3 meaning that the drug has a low potential for abuse and that it has accepted medical use.

Frank Sapienza (DEA) commented: "We didn't know that it was being used in therapy sessions."

CHAPTER 3: DESIGNER DRUGS

The term 'designer drugs' used in The Analogue Act of 1986, is so vague and misleading that its interpretation has been subject to much debate; and I speculate will continue until a more clarified law is written. The term analog used in chemistry is so infinite; it may include homologs, congeners etc. in reference to a parent substance. The term analog, in chemistry, differs from the term analogue, in the Analogue Act, by the fact that the legalese term, analogue, lacks a scienter.

On May, 1, 1986, a hearing was held before the Subcommittee on Crime of the Committee on the Judiciary House of Representatives, to review the problem of 'designer drugs.'

Hon. William J. Hughes was presiding. Present were Representatives Hughes, Smith, Staggers, McCollum, Lungren, Shaw, and Gekas. Staff Present were: Hayden Gregory, counsel; Eric E. Sterling and Edward O'Connell, assistant counsel; Charlene Vanlier Heydinger, associate counsel; Phyllis Henderson, clerk.

I will take various excerpts from the transcripts (except where noted) to give the reader some insight into what went into the creation of the Analogue Act of 1986.

Mr. Hughes: "Today the Subcommittee on Crime is continuing its examination of the problem of designer drugs. Two years ago, in the course of our examination of the diversion of controlled substances from medical purposes to the black market, we looked at the problem of designer drugs such as the fentanyl analogs, and MPPP, which were causing death and paralysis, particularly on the west coast.

In conjunction with the DEA, we developed an approach to the problem that allows the Drug Enforcement Administration to schedule these substances on a very short time frame on an emergency basis. This process for temporary scheduling freed DEA from the usual time-consuming requirement of scientific study that is the basis for determining what drugs ought to be controlled and in what schedule they can most approximately be controlled.

Since the law became effective, as part of the Comprehensive Crime control Act of 1984, DEA has used the authority 5 times to control some 13 substances....

A neurologist in San Jose, California, says that working with the Centers for Disease Control they have identified 400 persons who have been exposed to MPTP which causes Parkinsonism, and irreversible form of brain damage that is appearing. This doctor says that its is the tip of the iceberg. Seven of those persons, almost 2 percent of those known who are so severely ill, are permanently crippled and in danger of dying of the disease. Twenty of these persons were exposed, another 5 percent have mild symptoms of the disease. All of the young people exposed are at risk for developing Parkinson's symptoms. They are, as an investigator of the National Institutes of Health says, "walking time bombs." And now we are seeing people who have used the drug 2 years ago beginning to exhibit symptoms. We are facing a potential public health crisis that may make our current drug abuse problems look mild." (pg. 2)

Rudy M. Baum: "The fentanyl analogs make up one of three classes of drugs that generally have been lumped together as designer drugs. Analogs of another, chemically distinct narcotic - meperidine - make up a second class. The third class contains a single member, 3,4-methylenedioxymethamphetamine (MDMA), which for a number of reasons, probably should not be designated a designer drug."

(Baum 1985, page 8)

Rudy M. Baum: "Henderson coined the term "designer drugs" specifically in reference to the fentanyl analogs he was analyzing... For a variety of reasons, Henderson believes that a single "world class medicinal chemist" has been responsible for the various fentanyl analogs that have appeared... Henderson bases his assessment that a single, highly sophisticated chemist has been responsible for all the fentanyl analogs that have appeared..." (Baum 1985, page 8 & 10)

Henderson: "the quality control is really remarkable. These aren't garbage drugs. They are well made, with very few impurities, and the doses are uniform." (Baum 1985, page 11)

"In a DEA investigation begun about a year ago (1985), Kenneth Baker, a California chemist operating a clandestine laboratory, was identified as a manufacturer and distributor of 3-methylfentanyl, a drug which was scheduled pursuant to the emergency scheduling process. By the time the laboratory search took place (only six weeks after the start of the investigation), Baker had discontinued his production of 3-methylfentanyl but had produced substantial quantities of eight other fentanyl analogs. Unfortunately, however, not one these analogs had been scheduled under the Controlled Substances Act. The search revealed that Baker had obtained information on the scheduling of drugs by the Drug Enforcement Administration, presumably so that he could tailor his production to stay ahead of the scheduling process.

When it was learned that the drugs found in Baker's laboratory were not controlled substances and that charges could not be brought under the Controlled Substances Act, prosecutors determined that some means should, never less, be found to prosecute Baker and his co-conspirators. The Federal Food, Drug, and Cosmetic Act was reviewed for relevant provisions. In a multi-count indictment filed on March 20, 1986, Baker and others were charged with violating provisions of the Federal Food, Drug, and Cosmetic Act, including manufacturing a drug without registering drugs, with intent to defraud." (p. 31)

Letter from John C. Lawn to Edwin Messe III: "In one instance, a PH.D. chemist employed by DuPont Chemical Company prepared substantial quantities of fentanyl analogs in that company's laboratories. He attempted to locate distributors for these substances and was apprehended by DEA agents after he attempted to pick up payment for fentanyl analogs delivered to an undercover agent." (p. 146)

Mr. Lungren: "At the same time, I don't wish to suggest that we should rely solely on a death count as a measure of the threat that these drugs pose to our society. Mere statistics fail to express that misery perpetrated by contemporary Dr. Frankensteins who are transforming human beings into chemical zombies." (p. 3)

Mr. Lungren's statement specifically refers to deaths related to overdoses from high doses of narcotic analogs and contaminated 1-methyl-4-phenyl-4-propionoxy-piperidine (MPPP) (a narcotic analgesic) with the neurotoxic 1-methyl-4-phenyl-1,2,3,6-tetahydropyridine (MPTP). This accidental contamination resulted in a new and better understanding of Parkinson's Disease mechanisms for the scientific community. In rat tests this contaminant was not neurotoxic. It is unfortunate that narcotic addicts could not obtain legal narcotics with rehabilitation which is the true cause of their deaths (Opiods in Mental Illness 1981).

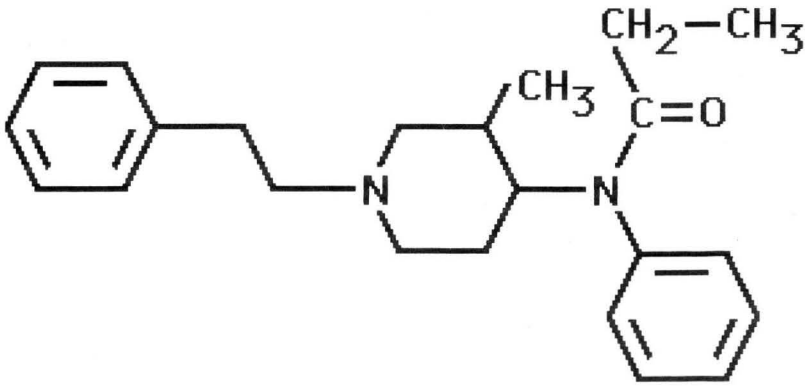
Mr. Lungren's concern is that we should not rely solely on a death count as a measure of the threat. Hundreds of thousands of Americans are injured each year by FDA approved drugs. Elderly people and the mentally ill continue to be abused, and tortured with dangerous psychiatric drugs. Families continue to suffer the consequences of unsafe FDA approved drugs, as authorities turn their backs to this epidemic in our country. Society pays the price for both dangerous (FDA approved and unapproved) drugs and inadequate drug development in this nation.

With the passage of the analogue law no further development of medications to help the mentally ill has taken place which has shown promise or relief without high cost and adverse effects. The passage of the Analogue Act has locked pharmaceutical development into the hands of those who have the most to gain from addiction, toxic reactions to substantiate continued drugging of the ill.

Drugs and nutrients which have been found to be helpful to those afflicted are unpatentable (orphan status) hence remain undeveloped and, in many cases, out of reach for those who are most in need.

Larry Smith: "We need to be proactive rather than reactive. That is why I support legislation to change the definition of the crime being committed. The legislation which I have introduced would change the illegality from the substance itself to the effect this substance has on an individual." (pg. 7)

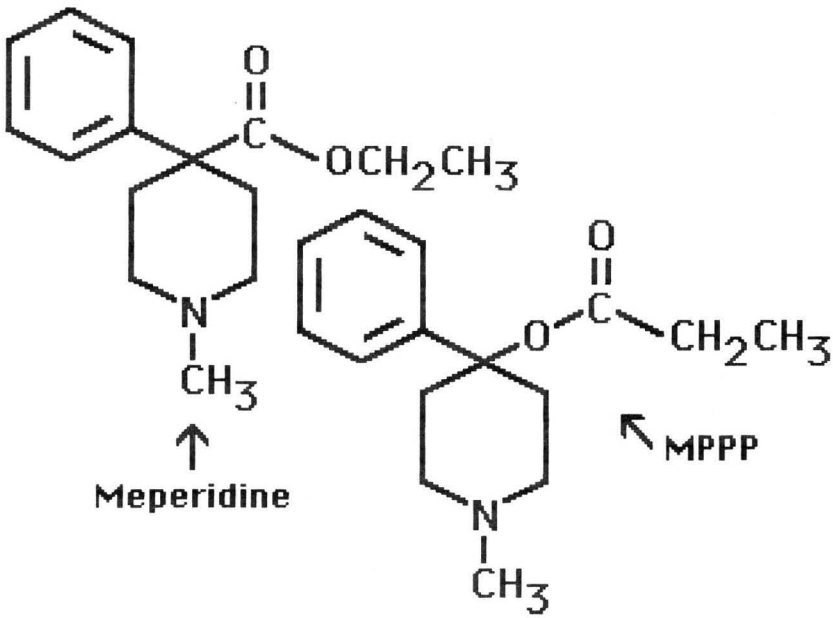
Neuroleptics (major tranquilizers) are used to induce psychosis and catatonia in patients following a malpractice. It is also used against women by medical staff so that they can rape female 'mental' patients with no resistance. Does this torturous action qualify as an illegal 'effect' under Larry Smith's new designed law?



3-Methyl-fentanyl

Dr. Schuster: "Over the past decade, the illicit use of meperidine has increased when heroin became scarce. Two other designer drugs with pharmacological effects similar to heroin have been identified and found to be similar in structure to meperidine. These two analogs, 1-methyl-4-phenyl-4-propionoxypiperidine (MPPP) and 1-(2-phenylethyl)-4-acetyloxypiperidine (PEPAP), have been shown in analgesic tests by NIDA to be many times more potent than meperidine....

The abuse of MPPP was first reported in the Washington, D.C. area in 1976, when a 23 year old man was referred to the NIMH for evaluation after exhibiting symptoms of Parkinson's Disease. A known drug user, he had used the meperidine analogue MPPP which he himself had manufactured. Since he was able to provide the chemical formula and procedures he had followed to produce the MPPP, it was discovered through subsequent analysis that he had inadvertently created the substance MPTP (1-Methyl-4-phenyl-1,2,3,6-tetahydropyridine) as a side product in the synthesis. Only the most stringent chemical controls would prevent some production of MPTP during the intended production of MPPP."



"(1-(2-phenylethyl)-4-phenyl-4-acetoxy-piperidine), (PEPAP), is a recent addition to the street scene, having been identified by the DEA in confiscations in California in 1985, and in the form of a precursor in a lab arrested in Texas in 1984. Its action is substantially similar to that of MPPP and, just as MPTP results from the production of MPPP, PEPTP from the production of PEPAP although preliminary research indicates it does not have the devastating neurotoxic properties of MPTP." (p. 43-44)

Charles B. Rangel: "Designer drugs are subject to no quality controls on potency or purity, thus exposing users to unknown dangers... The clandestine manufacture of controlled substance analogs was first encountered in the late 1960's, with several hallucinogenic drugs similar to LSD. In the 1970's, chemical analogs of PCP were prevalent. However, it was in the 1980's, with the creation of extremely potent analogs similar to heroin, or "synthetic heroin," that the real crisis developed."

(pgs. 12-13)

Although analogs of controlled substances have always been used in research, few entered the illicit market. Many of the analogs were not controlled as their appearance was sporadic. The PCP congeners that Mr. Rangel is discussing were not popular and were considered dangerous by many drug users. The drug was being sprayed on marijuana and also tableted and sold on the street. I was talking with a DEA agent concerning a PCP type molecule that had appeared on the street. I had received several reports of toxic reactions from individuals expecting pleasurable effects. I stressed that these molecules should be scheduled as they were dangerous especially at the dosage that was being distributed. The agent mentioned that these molecules would be scheduled soon. He also mentioned that every time that they scheduled one analog another would appear and were causing problems for law enforcement and dangerous to anyone who took these drugs.

It has been theorized that PCP congeners that bind to mu opiod receptors may have creativity enhancing effects. The major obstacle with phencyclidine type molecules is that elevated dosages have effects which can be dangerously sedating and hallucinogenic, resembling psychosis inducing 'chemical straight jackets' (neuroleptics).

Lawton Chiles: "It is interesting to note that some of the labs for designer drugs in California were broken up not by law enforcement people, but by organized crime people, because they felt it was interrupting their sales and distribution that had been set up for heroin, for the illegal drugs that come in. Now at what stage do those same organized crime people decide hey, wait a minute, we don't need to break up their labs, we will merge with them, so to speak. Will buy the small company. We will take it on and we will put it into our operation. That is where I think the real potential danger is." (p. 24)

Organized crime is always interested in recruiting chemists to 'cook up bathtub drugs' for them, generally these groups are not interested in 'designer molecules'. Organized crime syndicates have unlimited pipelines for narcotics from international smuggling groups.

John White: "The National Association of Retail Druggists (NARD) represents owners of more than 30,000 independent pharmacies, where over 75,000 pharmacies dispense more than 70 percent of the nation's prescription drugs. Together they serve 18 million persons daily.

We were concerned that the emergency scheduling authority, as originally drafted, was far too broad, and we were pleased when the Chairman and his colleagues agreed to a modification... ... which could in no way deny due process to the retail pharmacists we represent, who have numerous controlled substances with approved medical usefulness in their inventory." (p. 197-198)

Mr. Hughes: "If you look at the data, the Dawn reports, upward of 75 percent of the overdoses and deaths are caused by prescription drugs-the diversion of prescription drugs into the illicit markets. It is big business in this country."

"A few years ago we had diversion investigative units. They were phased out in that 1981-82 round, as you well know." (p. 20)

The enforcement of laws against drug diversion by physicians, pharmacists, and detail men was made a responsibility of the states. Law enforcement at the state level (in most states) are not trained, equipped, or even want to be bothered with investigating script doctors. Funding to investigate script doctors was cut from the DEA (1983). One third of street drugs come from practitioners, yet the DEA's hands are tied by political agendas, which are backed by campaign contributions from pharmaceutical firms, medical associations and all those who benefit from the drugging of America.

The following law went into effect in 1986 primarily to curb the barrage of homologs and analogs of the synthetic narcotics, meperidine, fentanyl that was being distributed by illicit networks as a replacement for street heroin. The most serious problem with a law controlling 'analogues' is that it inadvertently placed a blanket repression on the development, synthesis and study of research neurochemicals by private individuals, students and small businesses.

Controlled Substance Analogue Act of 1986
Treatment of Controlled Substance Analogues

"A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of this title and title 3 as a controlled substance in schedule 1."

Definition

Section 102 of the Controlled Substances Act (21 U.S.C. 802) is amended by adding at the end thereof the following:

"(32)(A) Except as provided in subparagraph (B), the term 'controlled substance analogue' means a substance-

"(i) the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule 1 or 2;

"(ii) which has a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule 1 or 2; or

"(iii) with respect to a particular person, which such person represents or intends to have a stimulant, depressant, or hallucinogenic effect on the central nervous system that is substantially similar to or greater than the stimulant, depressant, or hallucinogenic effect on the central nervous system of a controlled substance in schedule 1 or 2.

"(B) Such term does not include-

"(i) a controlled substance;

"(ii) any substance for which there is a an approved new drug application;

"(iii) with respect to a particular person any substance, if an exemption is in effect for investigational use, for that person, under section 505 of the Federal Food , Drug, and Cosmetic Act (21 U.S.C. 355) to the extent conduct with respect to such substance is pursuant to such exemption; or

"(iv) any substance to the extent not intended for human consumption before such an exemption takes effect with respect to that substance".

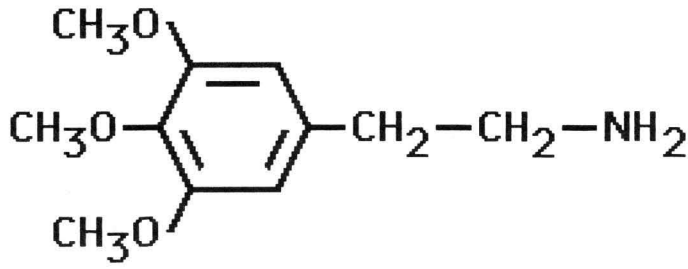
CHAPTER 4: THE TWO PRONG ATTACK: The first prong: "the chemical structure of which is substantially similar to the chemical structure of a controlled substance in schedule 1 or 2."

Dr. Hawks: "If I understand what you are getting at, if you mean can two compounds differ very slightly in structure and have quite different pharmacological properties--
Mr. Hughes: Yes.
Dr. Hawks: (continuing). Yes, that is very true. One primary example being the discovery some years ago of narcotic antagonists, where you can take the morphine molecule, make a small structural change to one position on it and have a morphine antagonist, so it has the opposite pharmacological effect...
Mr. Hughes: What determines the effect of a chemical compound?
Dr. Hawks: Its structure. As we have said, small structural changes can have, in some cases... can have tremendous effects on the pharmacology, or the pharmacological effect of that drug. And this is primarily based on structural changes, so structure is the main thing that causes the activity of the chemical.
Mr. Hughes: Do all chemicals in a particular chemical class have similar psychopharmacological effects?
Dr. Hawks: No." (pgs. 52-53)

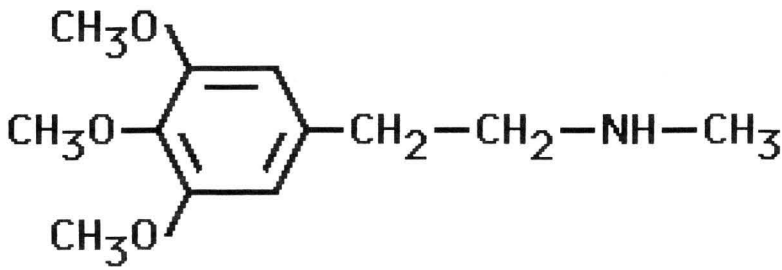
U.S. Patent Office will not grant a patent on a chemical described as 'substantially similar.' Chemicals indexed in chemical and scientific journals are not listed under headings of 'substantially similar,' because no such term exists in chemistry.

A Change in Structure; A Change in Activity.

In the phenylethylamine class of chemicals, a slight change in the structure will dramatically change the activity of a molecule. Examples: 3,4,5-Trimethoxyphenylethylamine (mescaline) is active. 3,4,5-Trimethoxy-N-methyl-phenylethylamine (an inactive molecule) is created when a methyl (CH_3) group is added to the amino group (NH_2) on the mescaline molecule.



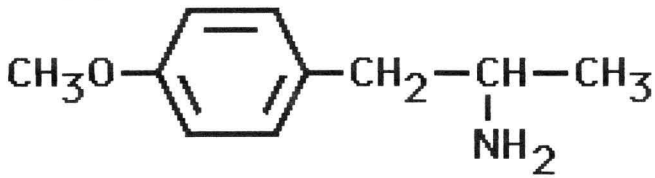
3,4,5-Trimethoxyphenylethylamine (mescaline)
M. F. $C_{11}H_{17}NO_3$ **M. W. 211.25**



3,4,5-Trimethoxy-N-methylphenylethylamine
M. F. $C_{12}H_{19}NO_3$ **M. W. 225.28**

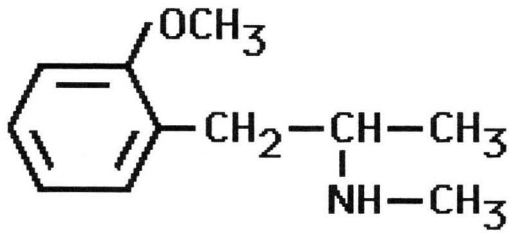
Substantial Differences in Amphetamines
A Change in Structure; A Change in Activity.

Here are a few more examples showing slight alterations in the molecular structure which produce substantially different biological and psychological effects.



4-Methoxyamphetamine
para-Methoxyamphetamine; (PMA)
M. F. $C_{10}H_{15}NO$ **M. W. 165.23**

Para-methoxyamphetamine is a hallucinogen; which was hypothesized to be endogenously formed during amphetamine psychosis (Smythies 1967). Testing concluded that this metabolic reaction did not occur (Angrist 1970).

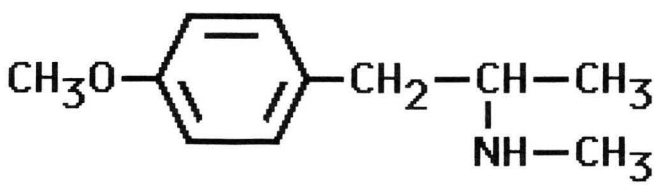


2-Methoxy-N-methylamphetamine
Methoxyphenamine

M. F. $C_{11}H_{17}NO$ **M. W. 179.25**

Moving the methoxy group (OCH_3) from the 4th carbon to the 2nd carbon on the phenyl group of PMA and adding a methyl (CH_3) group to the amino group (NH_2) results in a totally different chemical with a different molecular formula and a different molecular weight. 2-Methoxy-N-methylamphetamine is called methoxyphenamine.

Methoxyphenamine is a vasopressor. Without laboratory animal and human testing, its usefulness as a vasopressor would not have been discovered.

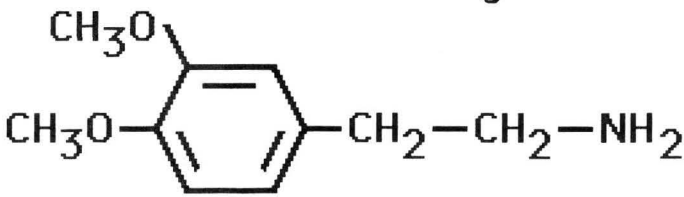


para-Methoxy-N-methylamphetamine
M. F. $C_{11}H_{17}NO$ **M. W. 179.25**

Para-methoxy-N-methylamphetamine is an active substance. Its effects are reported to be unlike DOM (4-methyl-2,5-dimethoxy-amphetamine) and amphetamine. It has the same molecular weight, the same chemical formula, but not the same molecular structure as methoxyphenamine.

Prior to testing a chemical (of a specific molecular structure) on laboratory animals and humans, we can not scientifically or accurately determine (without a substantial degree of uncertainty), assume or imply anything about the activity or non-activity of a molecule.

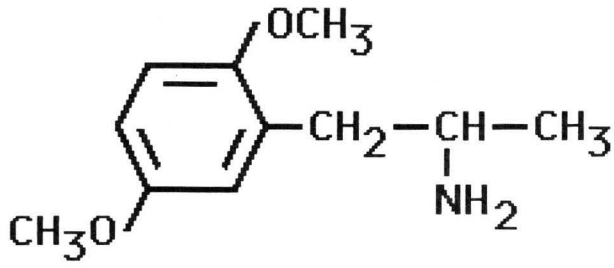
The Same Molecule, Different Species, Different Activity



3,4-Dimethoxyphenylethylamine

M. F. $C_{10}H_{15}NO_2$ **M. W. 181.24**

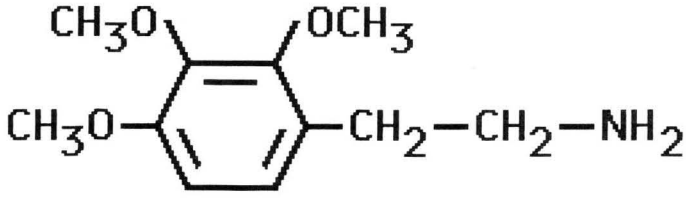
This molecule has been found in the urine of some schizophrenics. It was weakly active when tested in laboratory rats and inactive when tested in humans (Shulgin 1969). Meaning, if no humans would have tested this chemical it may have been assumed to be hallucinogenic and then assumed to be the endogenous cause of schizophrenia; which it is not. 3,4-Dimethoxyphenylethylamine is a neurochemical metabolite, not a biochemical marker in individuals with schizophrenia.



2,5-Dimethoxyamphetamine

M. F. $C_{11}H_{17}NO_2$ **M. W. 195.25**

2,5-Dimethoxyamphetamine, also called DMA, is inactive in laboratory rats (Smythies 1970) and also non-hallucinogenic in humans (Shulgin 1991). Rats metabolize many drugs differently than humans (Beckett 1970; Boissier; Smith 1970).



2,3,4-Trimethoxyphenylethylamine

M. F. $C_{11}H_{17}NO_3$ **M. W. 211.25**

2,3,4-Trimethoxyphenylethylamine is a positional isomer of mescaline (3,4,5-Trimethoxyphenylethylamine). It is inactive in normal subjects, but is hallucinogenic in schizophrenic patients (Slotta 1936) and is 'mescaline like' in rats. (Winter 1973)

"If you are familiar with the drug discrimination literature, you can get false-positives, and perhaps Professor Glennon will correct me if I am wrong, but I am not aware of false negatives." (Nichols 1989).

A misinterpretation of a molecule's activity can occur when tests are applied to inappropriate species.

The second prong: "effect on the central nervous system that is substantially similar to"

"3,4-Methylenedioxyamphetamine (MDA) is recognized as both d-amphetamine-like and DOM-like by rats trained to discriminate these drugs from saline.

3,4-Methylenedioxymethamphetamine (MDMA), is recognized only as d-amphetamine-like in the same tests.

3,4-Methylenedioxy-N-ethylamphetamine (MDE) and 3,4-Methylenedioxy-N-hydroxy-amphetamine, (N-hydroxy-MDA) in rodent drug discrimination studies with d-amphetamine and DOM as training drugs, do not generalize to either d-amphetamine or DOM. Based on this information alone it would appear that MDE and N-hydroxy-MDA are neither amphetamine-like stimulants nor DOM-like hallucinogens. These studies alone would further suggest that MDA, MDMA, MDE, and N-hydroxy-MDA have different abuse potentials."

(McClain 1989, pg. 31)

"Some phenyl-substituted phenylisopropylamines, such as MDA, PMA and MDMA, have pharmacological properties distinct from those of amphetamine or DOM. Therefore, prediction about the abuse liability of these compounds based on their similarities to or differences from classic stimulants (such as cocaine or amphetamine) or hallucinogens (such as LSD or DOM) may provide inappropriate results." (Sannerud 1989)

"INTENDED FOR HUMAN CONSUMPTION"

"A controlled substance analogue shall, to the extent intended for human consumption..."

Dr. Grinspoon: "Under the provisions of this law, a chemist who synthesized a new drug might actually be committing a crime by taking it. Self experimentation of this kind is the way in which most new drugs with valuable medical and scientific properties have been discovered.

It is true not only of synthetic drugs, but of drugs found naturally in plants. If the federal government makes it a crime to work with any new substance thought to have some undefined resemblance to a controlled drug, entire fields of therapeutic pharmacology may go undiscovered.

Many of the discoveries of new medicines and therapies have been made by scientists who try one thing and fail, and then try something else. The controlled development of analogs -- in effect, designer drugs -- is essential to the advance of pharmacology. Many of the antipsychotic and antidepressant drug discoveries of recent years are minor variations on a common molecular theme with similar effects. However, it is precisely the differences that are medically significant -- different potencies, different side effects, and most important, different therapeutic uses.

The same is true of analogs that do not belong to class of drugs with presently accepted therapeutic uses. One drug that has recently received some publicity is MDMA (3,4-methylenedioxy-methamphetamine). It is chemically related to several controlled substances. A number of researchers also take seriously its potential as an aid to insight and communication in psychotherapy, and they are interested mainly because its effects are not identical with those of the chemically related drugs.

When MDMA first appeared on the American scene in the early 1970's, it was known only to a few scientific and medical researchers; there was no significant illicit street use. It could not be patented, and no drug company was interest in it. If the proposed legislation had been in effect at that time, all research could have been brought to a hold. Since reputable physicians and scientists would not have been willing to become outlaws to work with MDMA, we would never have learned about its therapeutic potential. The small illicit market, on the other hand, would have been affected very little. Under the new law, if there are any therapeutically useful analogs of currently controlled drugs, we many never come to know of their existence.

The proposed "designer drug" legislation needs to be redesigned. Its language must be clarified or the exemption for scientific and medical research rewritten to protect the public against opportunist illicit drug profiteers without discouraging research on pharmacology in areas where early commercial application is unlikely."

(pgs. 83-85)

26 Year old female school teacher (rape victim): "Adam (MDMA) has helped me look at this suffering, to see my life as a whole and to understand it better. It has given me the courage to face the fears instead of ignoring them, to know that the most important thing is to struggle to trust myself. I don't know what my life will be like now, or how much I want to live, but I do know that the experiences I have gone through, even though painful, have also been full of tenderness and trust, and there is no longer this feeling of emptiness. I am not leaving a hospital with a prescription in my hand for anti-depressants. Rather, I'm leaving... with the courage to try to face my fears and to face life."

Ralph Metzer, Ph.D.: "One therapist has estimated that in five hours of one MDMA session clients could activate and process psychic material that would normally require five months of weekly therapy sessions." (Through The Gateway of the Heart; 1985, pgs. 51 & 2)

Angarola, Esq.: "It is also possible that some legitimate researchers could inadvertently violate the law by producing and investigating substances which may meet the criteria of the proposed amendments. As an example, there are substantial questions as to the interpretation of the term "intended for human consumption." Virtually every time a pharmaceutical company researcher synthesizes a compound, he or she is looking for something the will eventually be intended for human consumption after FDA approval. Would that researcher violate the law because of his long-term intention?" (pgs. 93-94)

Angarola, Esq.: "One representative testified to the fact that her company would not go forward in investigating a schedule 1 controlled substance unless the condition which was to be treated was life-threatening. The controlled substance analog legislation could have a similar chilling effect." (pg. 87)

Dr. Grinspoon: "Well, I am not a lawyer, but in fact, in the real world a drug company does not - you see if you're dealing with a drug let's say for the treatment of congestive heart failure and you can put an animal into congestive heart failure and you can see if this new digitalis or this digitalis analog improves the congestive heart failure. If you are dealing with a psychoactive drug, animals don't tell you that they feel less anxiety or feel less depression or what have you. And a drug company is not going to go ahead and put the thousands and thousands of dollars involved in getting an IND because in the real world some people in that drug company have tried that drug themselves.

Now I am sure these people are very experienced researchers. They know a lot about the chemical from which this analog arrived. They do it under very careful circumstances, take it in tiny doses at first, and so forth. But in the real world drug companies don't deal with psychoactive drugs unless they have some pretty good idea that let's say Valium is going to be a good antianxiety drug. That is the real world."

(pg. 109)

Mr. Lungen: "You have a specific complaint about the bill in which you say, first of all, criminal penalties are imposed without a requirement for evidence that anyone has been injured by a new analog or even that anyone has abused it... Some of these drugs that have been discovered in recent years have helped me get through pain, so I understand it like everyone else does. I don't want to stop the quest toward more science. My father is a doctor and I greatly respect the medical profession. In fact, I was in it until I ran into organic chemistry in premed, so I became a lawyer. [Laughter.]"

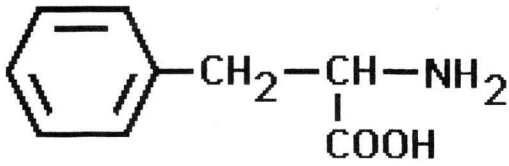
(pgs. 112, 114, 115.)

Dr. Tocus: "I can understand that if someone wants to know what the effect maybe, is it going to cause him to hallucinate, going to cause them to feel something, the investigator may take it one time to to see what is going to happen to his patients." (pg. 116)

Mr. Hughes: "I think that I am pretty much persuaded by the argument that is made that if you are talking about psychoactive drugs in particular that the only way you are going to find out just what impact they have upon humans is to try it." (pg. 117)

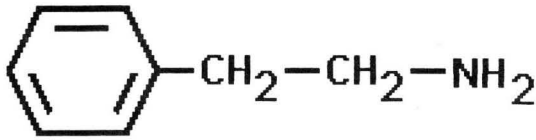
CHAPTER 5: THE REPRESSION OF NEUROCHEMISTRY

Many proteins are composed of phenylethylamine and tryptamine structures. Milk contains phenylalanine which is the carboxylic acid analogue of phenylethylamine. Phenylalanine could also be described as the des-methyl-carboxylic acid analog of amphetamine. When phenylalanine is decarboxylated it becomes phenylethylamine which is the des-methyl analog of amphetamine.



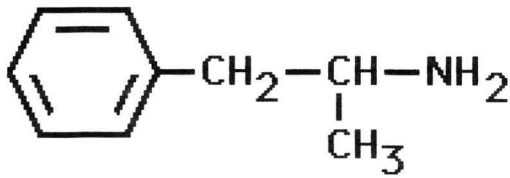
Phenylalanine

M. F. $C_9H_{11}NO_2$ **M. W. 165.19**



Phenylethylamine; (des-methyl-amphetamine)

M. F. $C_8H_{11}N$ **M. W. 121.18**



Amphetamine; (Alpha-methyl-phenylethylamine)

M. F. $C_9H_{13}N$ **M. W. 135.20**

Phenylethylamine is in chocolate. Chocolate is psychoactive. The effects are powerful enough that feeding a small dog too much chocolate can kill the animal. Phenylethylamine is responsible for some of the mood elevating effects of chocolate.

Many people give loved ones chocolate or to those who are sad to boost their spirits. Although individuals may say that they enjoy chocolate, that it brings pleasure to their lives; under the current law; (in strict interpretation of the law) would chocolate qualify as a controlled substance if used or "intended" as a drug (e.g. treatment for the blues)?

Mr. Trott: "A statute must also protect legitimate scientific research. That is, chemists should be free to conduct legitimate experimentation without fear of committing a serious federal felony." (p. 34)

The prohibitionist atmosphere has overloaded the courts as more serious crimes are not given the investigative attention and assets that they desperately need. The free reign given to law enforcement in many parts of the country under a guise of a 'drug war,' has undermined the foundations of civil liberties. Illegal drug money has corrupted many courts. Minimum mandatories have tied the hands of judges seeking the best possible solutions for those appearing before them. Impure & hazardous illegal drugs continue to be 'churned out' of make shift labs by criminals, as scientists are not permitted to study or develop safer substitutes.

From a business standpoint, intent is to produce a profit. From a scientific point of view, there is no intent, a scientist can not apply any preconceived ideas on a structure of an unknown non-existent molecule.

Scientists can not intent on the activity of any molecule as the molecule it self exhibits activity or non-activity regardless of what anyone thinks, wishes or contrives it will do, or could do.

The structural activity relationships of molecules are not precise, much is unknown. Chemists (psychopharmacologists) intend on creating better substances, with increased potency, less side effects (toxic effects), longer or shorter action, new therapeutic actions and/or new research applications: totally new chemicals. In simple terms, a scientist hopes and wishes for the best, (e.g. end human suffering, help to alleviate depression, disease, pain, etc.), but only the testing of a molecule in laboratory animals and humans will tell what the molecule actually does.

If chemists could predict what the effects of a contrived chemical structure would be, then drug companies would not be spending billions of dollars synthesizing, researching and developing new drugs. If chemists in chemical companies were so successful in their intent at 'designing' drugs and chemicals, is killing of the planet with toxic waste part of their intention? Everyone knows that you can't market products to a dead world.

The primary purpose of a scientist is to question, test, and continue researching; no action has any one specific purpose except that of seeking to transcend the unknown into the known. The most a scientist can do is hope to find something which will advance scientific knowledge which in turn will benefit the human race.

The very nature of neurochemistry involves the purchase of drug precursors as they are the precursors of many neurochemicals. Many chemicals that are used in the construction of neurochemicals are also used in clandestine laboratories, the only differences being the end products and their distribution. The very action of purchasing precursors places neurochemists under suspicion.

In all laboratory raids, a forensic chemist must be present to evaluate the chemicals and paperwork. A chemist is also necessary to identify chemicals which may be hazardous and to shut down reactions. Most laboratories have many chemicals. All individuals (law enforcement officers and suspects) are at risk of exposure to toxic chemicals if they are not contained; safety is paramount. Chemicals are safe as long as they are handled/stored and disposed of properly.

Mere suspicion is not a valid reason/grounds for the issuance of search warrants as this blocks scientific study, inquiry and advancement. 'Good intentions' as a reason for home invasions and confiscating of all scientific and technical paperwork as evidence is also not valid when there is a disregard for the scientific facts. The end does not justify the means to allow violation of 6th amendment rights.

Independent and law abiding neurochemists have been forced to purchase chemicals in a stealth matter to avoid suspicion and harassment from the state and federal government. These purchases are no different in the clandestine ways in which illegal drug chemists use to avoid detection by authorities.

The overbearing paranoia placed on neuroscientists is not conducive to a scientific atmosphere and hampers scientific inquiry and neurochemical development.

A FUNCTIONAL KNOWLEDGE OF CHEMICALS & CHEMISTRY

Society itself is primarily composed of those who are functionally ignorant of chemistry and research. Most individuals would not know the difference between dihydrogen oxide and deuterium oxide or the uses of either of these chemicals never mind more complex and unfamiliar chemical structures. This lack of scientific skills by average individuals is serious considering that technology is common place and is part of everything in our modern society. Those who are ignorant of science and technology are most likely to perceive it as a threat and repress development.

Most individuals are not fortunate enough to have a university library next door, wealthy enough to afford a modem, computer and be able to pay for access on data bases. All of this hinders the education of the individual, society and the evolution of science. A national toll-free data base access to all encompassing libraries of scientific and medical journals is necessary to foster independent study and to generate progressive development in the sciences. Large user accessibility, cross reference capabilities to vast amounts of information and rapid transfer of information are necessary.

When science is dynamic, students are attracted by curiosity, develop interest, get involved and want to learn more. Societies and national policies that invest in the sciences, reap profit from the advancement of technology. When governments and societies nurture, support and expedite public access to information and knowledge, the end result is a nation that can compete and is not handicapped in the world marketplace.

An exam was given to students world wide. The scores of American students were in the bottom third. Students in America are doing very poorly in sciences. Even Cuba has more literate individuals per capita than the United States.

Here are a few responses, (Parade Magazine 6/2/1991), from a 10th grade class when shown the poor test results (spelling, grammar and punctuation appear this way in the original letters):

"Not a Americans are stupid We just rank lower in school big deal."

"And if other countries are doing better what does it matter, their most likely going to come over the U.S. anyway?"

"Maybe that's good that we are not as smart as the other countries. So then we can just import all of our products and then we don't have spend all of our money on the parts for the goods."

"I am studying to be a lawyer and frankly I do agree with my parents when they say I have an attitude problem toward science."

When individuals are not educated enough to make decisions for themselves, they rely on the opinion of those who have the most to gain by representing their own interests instead.

"We don't know one millionth of one percent about anything." Thomas Edison

"The universe belongs to those who, at least to some degree, have figured it out." (Sagan 1974)

There are no lists of controlled substance analogues that are subject to control. Sapienza (DEA) and McClain (DEA) state: "The responsibility falls on DEA to advise attorneys whether or not a particular substance falls within the definition of a controlled substance analogue. Subsequently DEA staff or others may provide expert testimony regarding these matters." (McClain 1989)

The DEA are enforcers of the law. It would be dangerous to allow them to also interpret the law; this is an area for experts in science, research, law and a society based on individual liberties to develop, define and interpret.

The term analog to a chemist is a way of describing the relationship of a molecule's structure in comparison to another molecule's structure. This differs from the term used in the Controlled Substances 'Analogue' Act.

Analog does not mean that a molecule is inherently active or inactive; this is determined by testing the molecule in laboratory animals and in human subjects. An analog of a specific chemical does not inherently mean that the analog has an effect which is 'substantially similar' to the specific chemical or any other molecule for that matter. All the structural activity relationships that have been done to help predict the activity of theoretical molecules have proven to scientists how little is known and how much less can be predicted.

The transformation of technical terms to suit legalese is non-scientific and results in misinformation. A common example is lumping non-narcotic substances (e.g. marijuana) under a guise of narcotic. Narcotics are analgesic drugs (e.g. morphine, heroin, fentanyl, etc.) that are highly addictive. Classifying and portraying substances contrary to their actual effects on humans distorts their implications, if any, on society.

A misrepresentation of a drug's actions and effects is a non-factual foundation from which only further distortions and misconceptions will result.

Dr. Grinspoon: "Although the aim of the Senate bill and related House measures is a worthy one, I believe in its present form the legislation is seriously deficient in several ways that may be easily overlooked but are bound to have unfortunate effects on medical research. First of all, criminal penalties are imposed without a requirement for evidence that anyone has been injured by a new analog or even that anyone has abused it. Instead, the law relies on Justice Department officials and the courts to evaluate the molecular structure of a chemical or read the mind of its manufacturer. Even if the Justice Department and the courts were scientific authorities, they could not

properly do that. No one can know in advance the specific effects of a substance that has not yet been created, and the term "substantially similar" as used in the proposed law is both vague and unscientific. What may seem to be a small change in the chemical structure of a drug sometimes leads to a large difference in pharmacological effect." (pgs. 81 & 82)

Dr. Ellinwood: "...we (Research Council of the American Psychiatric Association) are aware of the difficulty in steering legislation in order to avoid after-the-fact legal action directed only piecemeal at a series on new compounds and at the same time avert an over inclusive, presumptive scheduling based on no facts other than the intent to distribute to humans. In more parabolic language, we understand your desire to avoid closing the barn door after the horses are out, yet hesitate to count your chicks before they hatch...

Points that we would like to have considered in developing the law and its interpretation:

... Means of establishing positive FDA and NIDA advocate procedures for facilitating appropriate legitimate human research on these drugs in order to balance the effects of needed restrictive legislation. These advocate procedures for establishment of a separate independent science-legal-ethics panel to expeditiously review procedures and to process proposal requests for research with drugs addressed in schedule 1 under the new law.

... Allow leeway for expediting significant, rigorous investigations on psychedelic drugs especially their therapeutic utility in certain mental disorders, and the nature of their potential for adverse mind altering effects. Research in this area has been so severely constricted that we have only limited knowledge of the parameters mediating the balance between a therapeutic and adverse outcome.

Means for allowing the expeditious approval of human research on psychedelic drug responses in appropriate research settings need to be facilitated by:

a) Establishment of a separate FDA panel of individuals from several science disciplines and persons concerned with legal and ethical aspects of drug research;

b) Psychedelic drug manufacture for research under the

auspices of NIDA or other appropriate agencies.

c) An approval for research on a time limited basis with extensions available only after appropriate feedback and progress reports." (pgs. 102-104)

A scientist: "What does 'substantially similar' mean? To me, that is almost a meaningless phrase." (Baum 1985)

Dr. Hawks: "One could think of words such as establishing credentials for people who might not have an IND and who have been doing research on certain kinds of compounds or for certain kinds of purposes, but you very quickly get into the kinds of things that people would bring up if they were taken to court to prove their innocence, or from the other side, to provide their lack of innocence. It almost seems like those kinds of subtleties are going to have to be worked out when this bill starts being used for enforcement and from interpretations from the courts and in the policy that results from that." (pg. 65)

Mr. Hughes: "We are a Nation of entrepreneurs. You would be surprised the number of experts I have in my congressional district on a myriad of subjects." (pg. 58)

Paul De Kruif: ... "great new medical things are rarely found in hospitals specifically endowed and designed to discover them; and great new medical things are rarely brought to light by scientists especially trained to uncover them." (A Man Against Insanity, p.11)

Mr. Hughes: "We want to make sure that we custom tailor the statute to reach those individuals who are creating designer drugs that end up on the marketplace being harmful to people.

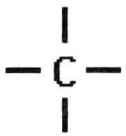
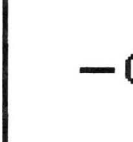
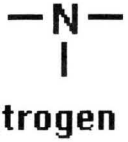
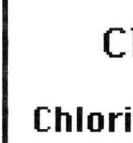
We don't intend to chill the research that takes place in laboratories or universities that is legitimate research. Or in private homes, if some entrepreneur is interested some aspect of life, human life or animal life. Frankly, I have a hard time understanding how we could determine, you know, what really intent is unless there has been a distribution." (pg. 59)

CHAPTER 6: THE CHEMISTRY

Organic and brain chemistry are far more exciting than inorganic and high school chemistry. Organic chemistry is dynamic, exciting and the 'juice' of the earth and brain.

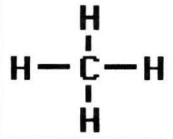
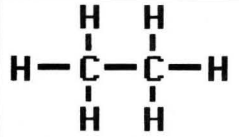
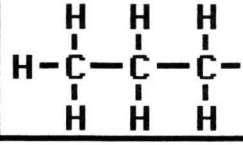
People who enjoy mystery, magic and quests usually enjoy organic chemistry. It is very easy once an individual understands the rules and learns how to look at molecules. It is much like a puzzle; an adventure.

Molecules are composed of elements. Each element bonds to a defined number of elements or functional groups. Bonds are drawn as a line from one element to another.

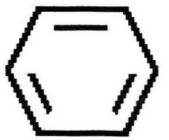
 Carbon (C) 4 bonds	Hydrogen (H) 1 bond	 Oxygen (O) 2 bonds
 Nitrogen (N) 3 bonds	 Bromine (Br) 1 bond	 Chlorine (Cl) 1 bond

Alkanes are a type of carbon-hydrogen chain.

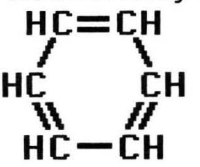
Name of Alkyl Chain	Alkyl Chain Structure
Methyl	$-CH_3$
Ethyl	$-CH_2-CH_3$
Propyl	$-CH_2-CH_2-CH_3$
Butyl	$-CH_2-CH_2-CH_2-CH_3$

Chemical	Structure	Alkane Chain	Formula
Methane (marsh gas)		CH_4	CH_4
Ethane		CH_3CH_3	C_2H_6
Propane (natural gas)		$CH_3CH_2CH_3$	C_3H_8

Benzene is a chemical that is found in the distillation of oil and of coal tar. It is used in chemical synthesis and also as a solvent. Like all molecules, benzene, can be looked at and drawn in many ways.



Benzene

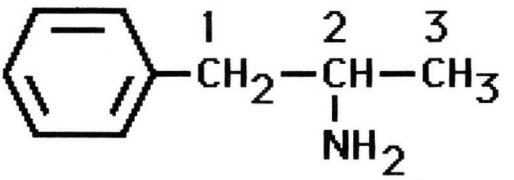


Benzene

Carbon atoms are numbered: 1 2 3

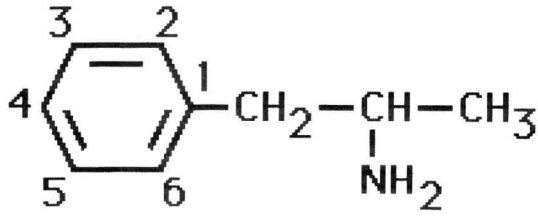
$CH_3—CH_2—CH_3$

so that we can describe what groups are attached where.



Chemical Names: Phenyl-2-aminopropane
Phenylisopropylamine
Generic Name: Amphetamine
Trade Name: Benzedrine

The phenyl group may also have substitutions and the carbon atoms are also numbered:



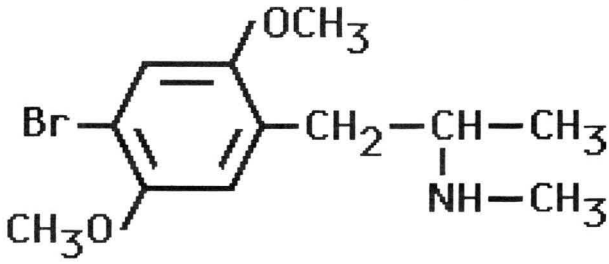
Functional (e.g. amino group; NH_2) groups are groups of elements that make up many molecules and are manipulated by the chemist in the construction of molecules:

Functional Groups That Contain Oxygen (R=Alkyl, etc.)

HO— Alcohol	—C=O \| O—H Acid	—C=O \| H Aldehyde
RO— Ether	—C=O \| O—R Ester	—C=O \| R Ketone

Molecular Weights; (Moles); The Keys of Chemistry

The molecular weight of a molecule is calculated by adding the atomic weights (from the periodic chart of the elements) of all the elements in the molecule.



4-Bromo-2,5-dimethoxy-N-methylamphetamine

M.F. $C_{12}H_{18}O_2N_1Br_1$ M.W. 288.18

Element	Atomic Weight	x	No. of Atoms	=	
Carbon	12.011	x	12	=	144.132
Hydrogen	1.0079	x	18	=	18.1422
Oxygen	15.9994	x	2	=	31.9988
Nitrogen	14.0067	x	1	=	14.0067
Bromine	79.904	x	1	=	79.904
			Molecular Weight = Total =		288.1837

The molecular formula of 4-bromo-2,5-dimethoxy-N-methyl-amphetamine is $C_{12}H_{18}O_2N_1Br_1$ Its molecular weight (one mole) is 288.1837 grams. Chemistry uses the metric system. Weights are in grams. Temperatures are in Centigrade.

References: Handbook of Chemistry and Physics; Merck Index.

The Reactions

The following text contains an overview of many reactions that are used in producing psychoactives, inactives, neurotransmitters, neurotoxins, unknowns and precursors to research chemicals.

Chemical reactions have specific as well as non-specific attack sites on a molecule or element. By products of reactions are distilled or extracted from trailings and recycled. Depending on what is run through a specific reaction will determine what will be the product or products. Theoretical yields can be achieved in some chemical reactions. In many reactions, yields are significantly lower and isomers are produced.

It is important to have a analytical testing laboratory analyze chemicals every step of the way in the construction of the final end product. This is necessary to determine:

1) completeness of the reactions.
2) by products which are being created and can be recycled. Controlled substance by products must be destroyed as described under CFR 21 § 1307.22
3) identification and purity of the end product.

Chemistry is a lot of fun. It is a pure science and has predictable results that can be duplicated. Chemistry must be given the respect that it deserves. Like anything, safety precautions must be followed when working with chemicals. Those that do not follow appropriate safety precautions will quickly learn respect when a reaction goes haywire.

The prankster that envisions haphazardly mixing chemicals together like a mad scientist will learn respect through fear. Improper ventilation will result in the asphyxiation of the chemist. Improper preparation techniques will result in an impure mush of unknowns, exothermic reactions, fire and explosions. Common sense has a lot to do with safety in the laboratory setting. You wouldn't pump gas into your car with a cigarette hanging out of your mouth. A simple mistake such as unplugging an electric plug in a room that contains a solvent vapor can result in explosion.

Safety smocks, gloves and proper face shields should always be worn in the laboratory whether working on a reaction or in the presence of someone who is. A safety shower should be tested before doing a reaction to make sure that it is running properly. A safety shower is a necessary protection for someone who has spilled chemicals on themselves.

Although I have mentioned a few safety precautions, there are many more, too numerous to cover because of the variabilities with any experiment. I would strongly suggest to anyone, who is interested in learning proper chemical procedures, to take a course in inorganic chemistry. There is nothing that can replace the hands on experience gained through the help of a patient and experienced instructor.

I describe the synthesis of molecular series in a generalized scope because of the versatility of reactions. I strongly recommend that any one interested in a particular reaction read all references cited in book. Journal articles contain specific reagent quantities and a more detailed description of syntheses. Those interested in studying the preparation of any specific molecule must also continue with a thorough search of the periodicals.

Laboratory setups are not described. This reference guide provides an over view of various syntheses and should not be misconstrued as a treatise or instruction manual. Information on organic laboratory setups and chemical syntheses can be obtained from several books included in the suggested reading section.

Legal as well as illegal chemicals are produced from the same precursors and many of the same immediate precursors. The primary reactions may only differ in the amount of chemicals added, temperatures and reaction times; and yet the end products may be very different. This is a problem for independent chemists in America who are currently researching brain chemistry.

"On July 17, 1990 President Bush issued a Decade of the Brain Proclamation, calling upon all public officials and the people of the United States to observe the decade with appropriate programs and activities. (from Decade of the Brain 1990 - 2000; Maximizing Human Potential; Subcommittee on Brain and Behavioral Sciences; pub. April 1991):

Several developments have converged to make the goals of the Decade of the Brain attainable in the 1990's:

1) The science essential to an understanding of the brain has matured dramatically in the past few decades, permitting greater transfer of basic laboratory knowledge to practical applications.
2) The methodologies and research tools to examine the processes at work in the healthy and unhealthy brain are rapidly maturing.
3) Medical, research and other professional institutions and organizations in the United States and countries around the world are strongly committed to advancing our understanding of the human brain.

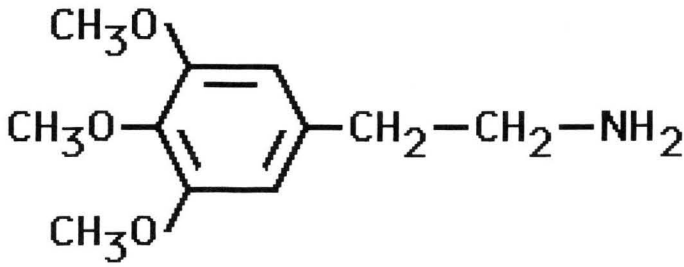
To pursue all possible leads about the brain in health and disease, the United States supports and works with scientists in institutions throughout the world. International programs take many forms:

1) joint research conducted under country-to-country agreement,
2) efforts involving multinational organizations,
3) research grants and training programs,
4) collaborative research projects uniting individual U.S. scientists and foreign colleagues, and
5) international meetings to share knowledge.

Investigators will build on the growing foundation of information about brain-drug interactions to develop medications, techniques and approaches that can be utilized to:

1) block the effects of abused drugs,
2) reduce the craving for abused drugs,
3) reduce the withdrawal effects of drug addiction,
4) reverse the toxic effects of abused drugs,
5) develop substitutes for abused drugs with less toxic effects, and
6) prevent the initiation of drug use."

CHAPTER 7: PSYCHOACTIVE SUBSTANCES MESCALINE & OTHER PSYCHOACTIVE PHENYLETHYLAMINES



Mescaline

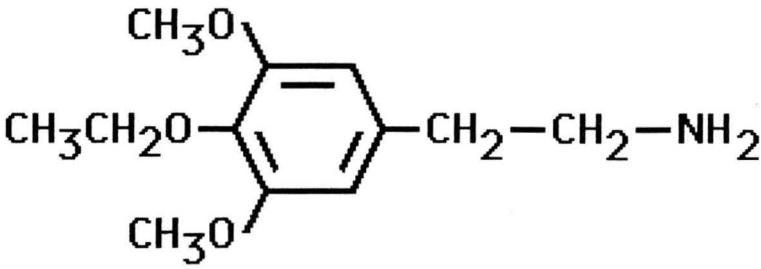
3,4,5-Trimethoxyphenylethylamine is the chemical name for mescaline. Mescaline is the psychoactive alkaloid of the peyote cactus (*Lophophora williamsii*). It was first isolated by Arthur Heffter in 1896. In 1897 Ernst Späth determined the correct chemical structure of mescaline to be 3,4,5-trimethoxyphenylethylamine. Späth succeeded in synthesizing this molecule in 1919.

Lophophora includes two species, *williamsii* and *diffusa*. *Lophophora diffusa* primarily contains phenolic alkaloids. Several other species of cacti contain traces of mescaline. A hallucinogenic South American drink called cimora is made from the San Pedro cactus (*Tricherocerus pachanoi*). Some *Tricherocerus* species contain traces of mescaline.

The nauseousness and vomiting provoked by consumption of mescaline containing cacti guarantees that their impact on society will remain as mere horticultural collectables.

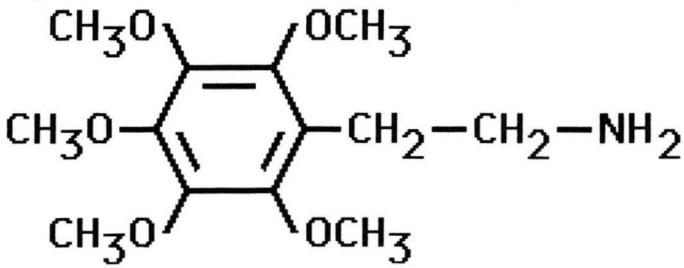
Mescaline is a weakly active hallucinogen (entheogen). At a dosage of 400 mg. it produces nausea, vomiting and colored visualizations. Mescaline has not been available as a street drug because it is neither economically feasible to extract from natural sources nor to produce synthetically.

Some substituted phenylethylamines and many substituted amphetamines are more active and less costly to produce than mescaline. Precursors for other psychoactive phenylethylamines and amphetamines are readily available from nature and their altered structures produce less nausea. The demand for mescaline is limited to scientific research (Shulgin 1973).



3,5-Dimethoxy-4-ethoxyphenylethylamine

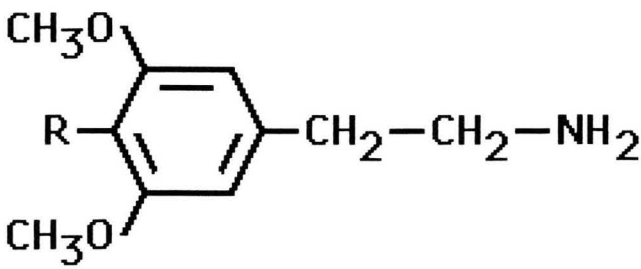
The hallucinogenic action of mescaline is associated with substitutes on the 3,4,5 positions. By replacement of the 4-methoxy group with longer chains such as ethoxy, propoxy, will produce psychoactive molecules such as 3,5-dimethoxy-4-ethoxy-phenylethylamine which is more active, lack visual activity and produce less nausea than mescaline. 3,5-Dimethoxy-4-ethoxy-phenylethylamine, also called escaline, is active in human subjects at 60 mg. 3,5-Dimethoxy-4-propoxy-phenylethylamine, also called proscaline, is active in human subjects at 60 mg.



Pentamethoxyphenylethylamine

The addition of methoxy groups such as 2,6-dimethoxy to the mescaline molecule while leaving the 3,4,5-positions intact should retain activity.

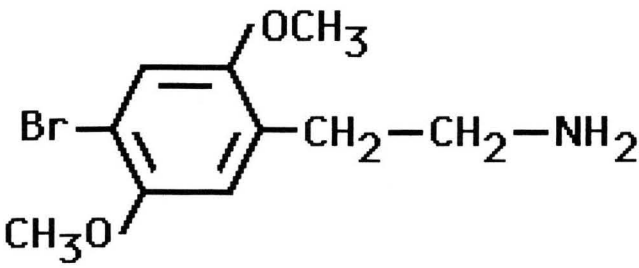
Series of molecular substitutions are described in the following way to condense space. This allows the reader to conveniently see differences and similarities within a series of structures.



4-Substituted-phenylethylamines

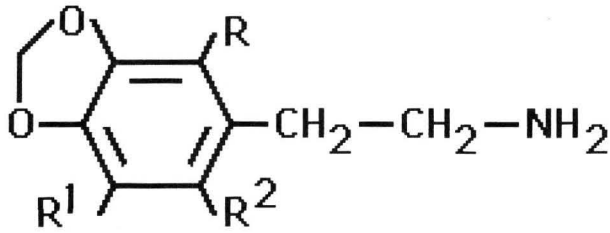
Substitutions	**R =**
3,5-Dimethoxy-4-propoxy	R = $OCH_2CH_2CH_3$
3,5-Dimethoxy-4-methyl	R = CH_3
3,5-Dimethoxy-4-ethyl	R = CH_2CH_3
3,5-Dimethoxy-4-propyl	R = $CH_2CH_2CH_3$
3,5-Dimethoxy-4-Br	R = Bromine
3,5-Dimethoxy-4-Cl	R = Chlorine

Replacement of the 4-methoxy group of mescaline with alkyl groups (e.g. methyl, ethyl) retains and increases activity compared to that of mescaline. 3,5-Dimethoxy-4-methyl-phenylethylamine has been noted to produce rage reactions in cats. The replacement of the 4-methoxy group on mescaline with halogens such as bromine or chlorine will also produce molecules with psychoactivity.



4-Bromo-2,5-dimethoxyphenylethylamine

4-Bromo-2,5-dimethoxyphenylethylamine, also known as 2CB, has been shown to be psychoactive. It produces MDA like effects at low dosages. Mescaline over tones and stimulant side effects have been experienced with elevated dosages. The dosage range for 2CB has been reported from 5 to 10 mg. This molecule possesses substitutions on the 2,4,5 positions of phenyl group of the phenylethylamine molecule. 2,4,5 Substituted amphetamines have been found to possess powerful psychoactivity in comparison with mescaline or other 3,4,5-substituted psychoactives.



3,4-Methylenedioxy-Substituted Phenylethylamines

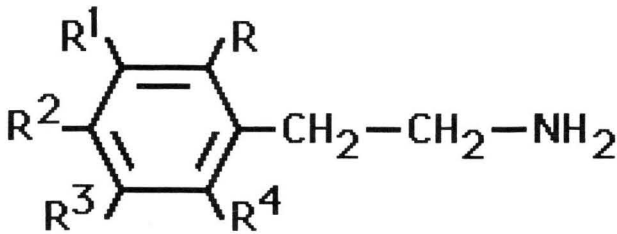
Substitution	R	R^1	R^2
2-Methoxy	OCH_3	H	H
5-Methoxy	H	OCH_3	H
6-Methoxy	H	H	OCH_3
2,5-Dimethoxy	OCH_3	OCH_3	H
2,6-Dimethoxy	OCH_3	H	OCH_3

The replacement of the 3,4-dimethoxy group in mescaline with a 3,4-methylenedioxy substitution abolishes activity and produces a mood elevator that is without visual activity.

3,4-Methylenedioxy-5-methoxyphenylethylamine is the chemical name of lophophine. At a reported dosage of 150 mg. in human subjects, the primary effects are mood elevation, euphoria and mild enhancement of color visual perception. The effects of this molecule resemble that of classical mood elevators.

3,4-Methylenedioxyphenylethylamine is not hallucinogenic and has antitussive activity. 4-Chloro-, 3-methyl-, 4-methyl-, and 3,4,5-trimethylphenylethylamine produce rage reactions in cats.

Many of the substituted phenylethylamines are inactive. This allows researchers to study differences between the structures of inactive and active molecules to formulate theories and experiments to better understand the biochemistry and neuronal mechanisms of the brain.



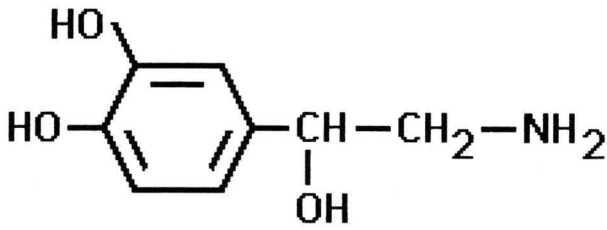
Substituted Phenylethylamines

Substitution	R	R^1	R^2	R^3	R^4
3,4-Dihydroxy	H	OH	OH	H	H
3,4-Dimethoxy	H	OCH_3	OCH_3	H	H
4-Hydroxy	H	H	OH	H	H
2,4,5-Trihydroxy	OH	H	OH	OH	H
2,3,4-Timethoxy	OCH_3	OCH_3	OCH_3	H	H

3,4-Dimethoxyphenylethylamine is weakly active in rats and is inactive in humans. At a dosage of 1 gram it failed to produce any effects in human subjects. It has been found in the urine of some schizophrenics and also occurs in many cacti. N-Methyl substituted phenylethylamines are also reported to be inactive.

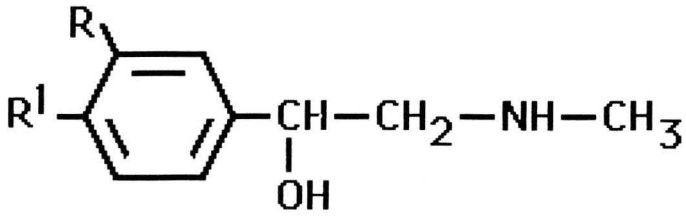
3,4-Dihydroxyphenylethylamine is a neurotransmitter called dopamine. 4-Hydroxyphenylethylamine is called tyramine and occurs in cheese, ergot and mistletoe. It is an endogenous precursor to dopamine. 2,4,5-Trihydroxyphenylethylamine is a neurotoxin.

2,3,4-Timethoxyphenylethylamine is inactive in normal subjects, but is hallucinogenic in schizophrenic patients (Slotta 1936) and is mescaline like in rats (Winter 1973).



Noradrenaline

3,4-Dihydroxy-1-(phenyl-2-aminoethanol) is the chemical name for noradrenaline. Noradrenaline is also called norepinephrine. It is a neurotransmitter. Norepinephrine is a constituent in many cacti and some plants namely banana, plantain, potato and *Portulaca oleracea*.



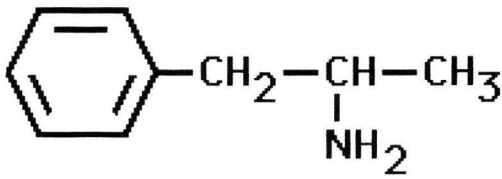
3,4-Substituted-1-(phenyl-2-methylaminoethanol)

Chemical	Substitutions	R	R^1
Adrenaline	3,4-Dihydroxy	OH	OH
Normacromerine	3,4-Dimethoxy	OCH_3	OCH_3
Synephrine	4-Hydroxy	H	OH

Adrenaline is also called epinephrine. It is a neurotransmitter. It occurs in many cacti.

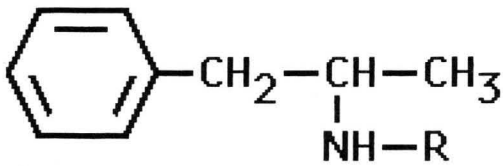
Normacromerine and synephrine occur in cacti. Synephrine also occurs in *citrus* species. It is used as a nasal decongestant.

AMPHETAMINE, METHAMPHETAMINE & SUBSTITUTED PHENYLISOPROPYLAMINES



Amphetamine

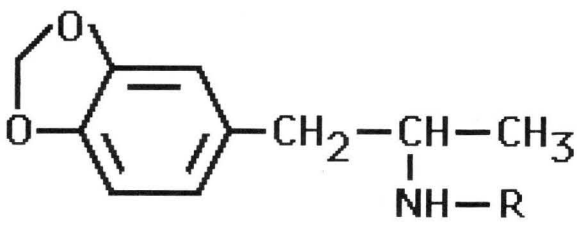
Amphetamine is a central nervous system stimulant (Kefalas). It is used to increase alertness and as an anorexic. It is prescribed for exhaustion, narcolepsy and to hyperactive children. Amphetamine is also called phenylisopropylamine. It is active at 5 mg.



N-Alkylamphetamines

Chemical Name	R	N-Homolog
Amphetamine	R = H	
Methamphetamine	R = CH_3	N-methyl
Ethamphetamine	R = CH_2CH_3	N-ethyl

Methamphetamine (N-methylamphetamine) is a more powerful central nervous system stimulant than amphetamine. Ethamphetamine (N-ethylamphetamine) is also a central nervous system stimulant. Its actions are less stimulating than that of amphetamine.



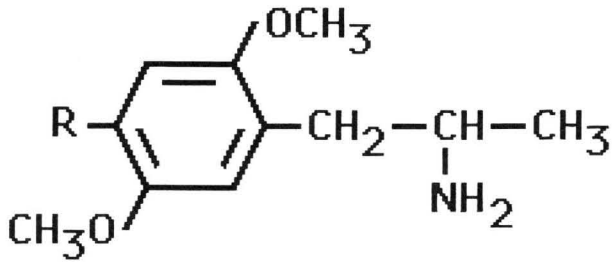
3,4-Methylenedioxy-N-alkylamphetamines

Abbreviated Name	R	Homolog
MDA	R = H	
MDMA	R = CH_3	N-methyl
MDEA	R = CH_2CH_3	N-ethyl
N-hydroxy-MDA	R = OH	N-hydroxy

MDA is the abbreviated name for a substituted amphetamine psychoactive called 3,4-methylenedioxy-amphetamine. It has been abbreviated as EA-1299 by the Edgewood Arsenal, U.S. Army Chemical Warfare Service. MDA is a stimulant empathogenic drug. The reported dosage is between 50 to 200 mg. It produces mood elevation, bonding and empathy. The drug's actions last from 6 to 8 hours. MDA's actions are non-hallucinogenic in low dosages. This differs from most of the other substituted amphetamines which are hallucinogenic. L-MDA maintains self injection in monkeys (Beardsley 1986) (Lamb 1987).

MDMA is the abbreviation for 3,4-methylenedioxy-methamphetamine. It is the N-methyl homolog of MDA. It has been abbreviated in literature as MDMA, MDM and also EA-1475. The reported dosage for MDMA is between 50 to 250 mg. The average dosage is 150 mg. The drug's duration of action is 4 to 6 hours. It has less stimulating side effects compared to MDA. Both MDA and MDMA have been extensively used as adjuncts in psychotherapy (Bakalar 1990) (Greer 1983, 1986, 1990) (Naranjo 1967) (Smith 1985) (Turek 1974) (Through The Gateway of the Heart 1985) (Yensen 1976).

MDMA was patented in 1912 by E. Merck. The Army Chemical Center performed toxicological and behavioral studies of this drug during the 1950's. The report was declassified in 1967 and published six years later. The N-ethyl homolog of MDA is called MDEA. N-hydroxy-MDA is also active.

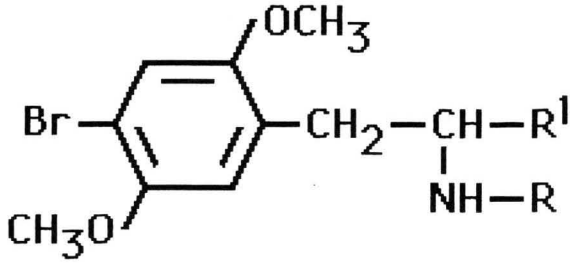


4-Substituted-2,5-dimethoxyamphetamines

Abbreviated Name	R	Tested Human Dosage
2,5-DMA	H	80 to 160 mg.
TMA-2	OCH_3	20 to 40 mg.
MEM	OCH_2CH_3	20 to 50 mg.
DOM	CH_3	3 to 10 mg.
DOET	CH_2CH_3	2 to 6 mg.
DOI	Iodine	1.5 to 3 mg.

The 2,4,5-substituted amphetamines possess powerful psychoactivity. 2,4,5-Trimethoxyamphetamine (abbreviated TMA-2) is hallucinogenic at a reported dosage of approximately 20 mg. in humans. 4-Ethoxy-2,5-dimethoxyamphetamine is called MEM. Its effects are empathogenic.

DOM is the abbreviation for a long acting hallucinogen called 4-methyl-2,5-dimethoxyamphetamine. It does not cause self-injection reinforcement behavior in monkeys (Hoffmeister 1975). The primary effects of DOET are MDA like. 2,5-DMA appears (see literature) to be non-hallucinogenic in both humans and in rats.



4-Bromo-2,5-dimethoxyphenylalkylamines

Abbreviated Name	R	R^1
2C-B	R = H	$R^1 = H$
DOB	R = H	$R^1 = CH_3$
N-Methyl-DOB	$R = CH_3$	$R^1 = CH_3$

4-Bromo-2,5-dimethoxyphenylethylamine (abbreviated names are 2C-B and also described as alpha-des methyl DOB) has an approx. dosage of 10 mg. in humans. It has an empathogenic effect in humans.

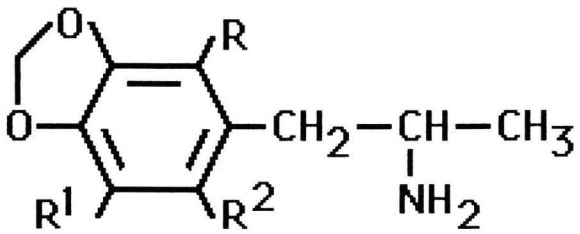
4-Bromo-2,5-dimethoxyamphetamine (abbreviated as DOB) has a reported dosage of 0.5 to 1.0 mg. in humans. It has an empathogenic effect in humans.

4-Bromo-2,5-dimethoxy-N-methylamphetamine has a reported dosage of approximately 5 to 10 mgs in humans. It is also empathogenic.

4-Bromo-2,5-dimethoxy-N-ethylamphetamine may also be active.

4-Bromo-2,5-dimethoxy-N,N-dimethylamphetamine is inactive in humans.

The primary action of 4-bromo and 4-chloro-2,5-dimethoxyphenylalkylamines is described as MDA like. The effects of DOB are long acting, six to twelve hours. Restlessness is the major side effect. At low dosages they produce euphoria, mood elevation and empathy (empathogenic). References: (Baltzly 1940a, 1940b, 1950) (Barfknecht 1971, 1978) (Knoll 1970)



Substituted-3,4-methylenedioxyamphetamines

Abbreviated Name	R	R^1	R^2
DMMDA	CH_3O	CH_3O	H
DMMDA - 2	H	CH_3O	CH_3O
MMDA - 2	H	H	CH_3O
MMDA - 3a	CH_3O	H	H
MMDA	H	CH_3O	H

2,5-Dimethoxy-3,4-methylenedioxyamphetamine is active in humans, at 30 to 75 mg. (abbreviated: DMMDA).

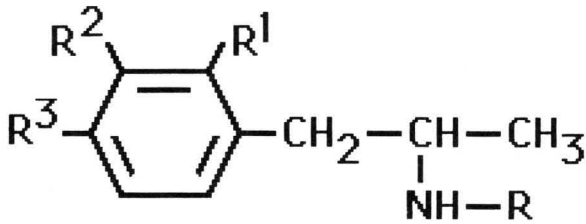
2,3-Dimethoxy-4,5-methylenedioxyamphetamine is active in humans, at 50 mg. (abbreviated: DMMDA-2).

2-Methoxy-4,5-methylenedioxyamphetamine is active at 25 to 50 mg. in humans (abbreviated: MMDA-2).

2-Methoxy-3,4-methylenedioxyamphetamine is active at 20 to 80 mg. in humans (abbreviated: MMDA-3a).

3-Methoxy-4,5-methylenedioxyamphetamine is active at 100 to 250 mg. in humans (abbreviated: MMDA). These substances produce euphoria, bonding, mood elevation and empathy (Shulgin 1967).

Amphetamine, methamphetamine, MDA, MDMA, p-chloroamphetamine, p-chloromethamphetamine and fenfluramine are all neurotoxic to serotonin axons in laboratory animals (Costa 1971) (Ricaurte 1989). Methamphetamine causes long lasting dopamine nerve terminal and nerve fiber destruction in rat brains. Pretreatment or post treatment with fluoxetine blocks neurotoxicity to serotonin axions (Battaglia 1988a) (Schmidt 1987). GABA-transaminase inhibitors also block neurotoxicity (Stone 1987).



Amphetamine	R	R^1	R^2	R^3
o-Methoxy	H	OCH_3	H	H
p-Methoxy	H	H	H	OCH_3
p-Methoxy-N-methyl	CH_3	H	H	OCH_3
p-Methoxy-N-ethyl	CH_2CH_3	H	H	OCH_3
p-Methoxy-N-hydroxy	OH	H	H	OCH_3
p-Chloro	H	H	H	Cl
p-Chloro-N-methyl	CH_3	H	H	Cl
m-Trifluoro-N-ethyl	CH_2CH_3	H	CF_3	H

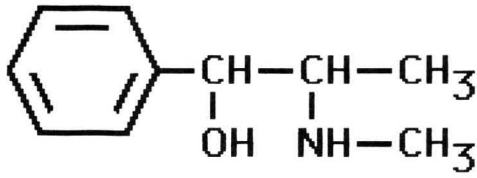
ortho-Methoxy-N-methylamphetamine is called methoxyphenamine. Methoxyphenamine is used as a vasopressor.

para-Methoxyamphetamine is hallucinogenic. The effects of para-methoxy-N-methyl-amphetamine, in rats, are unlike DOM and amphetamine.

para-Chloroamphetamine and para-chloro-N-methylamphetamine are both neurotoxic to serotonin axons, reduce both serotonin in the brain and 5-hydroxy-indole acetic acid in spinal fluid. They are used in research.

para-Chloro and para-bromomethamphetamine have been reported to be anorexic without an increase in motor activity (Kefalas 1962). meta-Trifluoro-N-ethylamphetamine is called fenfluramine. It is used as an anorexic (Beregi 1970). It is neurotoxic. It does not cause significant self-injection reinforcement in monkeys. Fenfluramine (Primetime Live 5/8/96) has been linked to primary pulmonary hypertension (incurable) causing death within 3 years. Fenfluramine was taken off the market (FDA) as it causes serious heart disease in approximately one in three patients (news sources).

Ephedrine Alkaloids

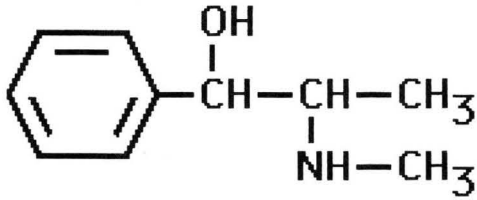


Ephedrine

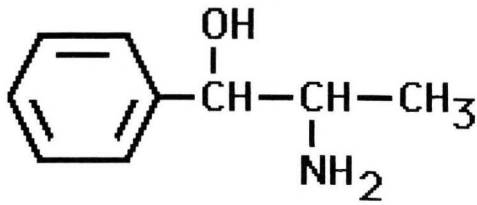
Ephedrine alkaloids are used throughout the world for their symptomatic actions. They have a wide variety of actions depending on their molecular structure and various substitutions. These molecules possess nasal decongestant, vasopressor (increase blood pressure), anorexic (appetite suppressant) and CNS (central nervous system) actions such as CNS stimulation (Chen 1929).

The Chinese herb Ma Hung (*Ephedra vulgaris*, *Ephedra sinica*, *Ephedra equisetina*) has been used for thousands of years as a symptomatic in China. It is the first natural source in which ephedrines were discovered. In 1887, a Japanese chemist by the name of Nagai isolated ephedrine from Ma Hung. Several isomers and analogs have been extracted from *Ephedra* species (Kanao 1927; 1930) (Nagai 1928). Ephedrine also occurs in the leaves of yew (*Taxus baccata*), in *Roemeria refracta* D.C. *papaveracoe* and also *Aconitum napellus*.

Many isomers (e.g. pseudoephedrine), homologs and analogs of ephedrine occur naturally as trace alkaloids in plants. These materials are produced synthetically (Manske 1929) (Wilbert) because it is more economical than extraction from natural sources. Pseudoephedrine is used as a nasal decongestant (Besson 1936).

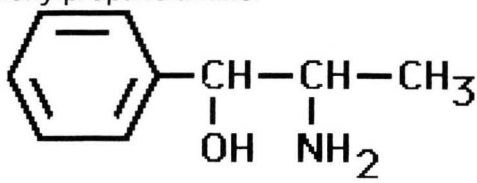


Pseudoephedrine



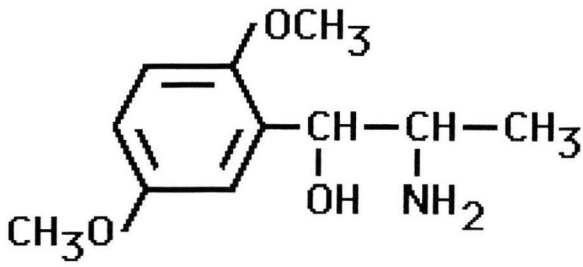
Cathine

Kathine, also called cathine (d-norpseudoephedrine), occurs (0.1 %) in the Arabian plant, *Catha edulis*. The leaves of this plant have been used (chewed for its stimulating affect) for thousands of years. Kathine has been identified in a South American tree called *Maytenus krukovii*. d,l-Norpseudo-ephedrine is used as an anorexic and CNS stimulant (Hofmann 1955; 1/6th as potent as d,l-amphetamine) (Horst-Myer 1959) (Kanao 1928). The dextro isomer has 6 times the stimulant action of the levo isomer (Hofmann 1955). Kathine is also an isomer of a common nasal decongestant and anorexic called phenylpropanolamine.



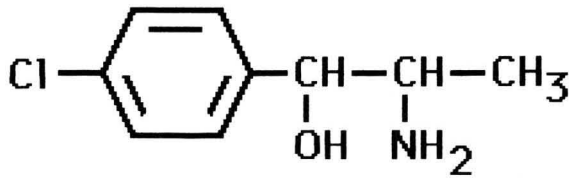
Phenylpropanolamine

Racemic phenylpropanolamine is also called dl-nor-ephedrine. Ephedrine alkaloids are relatively safe when used in accordance with dosage guide lines for short periods. Individuals with heart conditions, liver disorders or kidney disorders should not take these materials (Wilbert).



Methoxamine

Methoxamine is the generic name for 2,5-dimethoxy-phenylpropanolamine. It is used as a vasopressor (Morishita 1961).

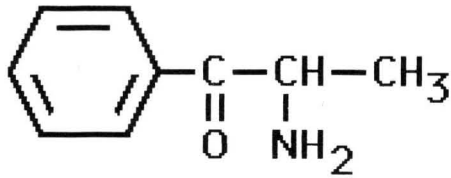


p-Chloro-norephedrine has been reported not to be neurotoxic (Smith, 1974). In preclinical reinforcement studies, phenylpropanolamine was not self administered by baboons.

Pseudoephedrine may cause birth defects (gastroschisis) if taken by pregnant women during their first trimester (Fackelmann 1995).

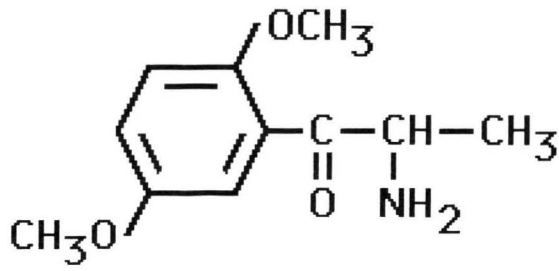
Ephedrine and pseudoephedrine can be reduced to produce methamphetamine. Phenylpropanolamine can be reduced to produce amphetamine.

AMINOKETONES



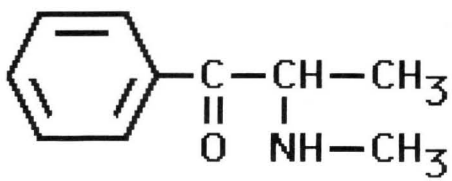
Cathinone

(S)-2-Amino-1-phenyl-1-propanone also called Cathinone, occurs in the Arabian plant, Catha edulis (Peterson 1980). The leaves are chewed for recreation and anti-fatigue properties (Nencini 1986). Cathinone has been found to have anorexic and stimulating effects in humans. It is equal in potency to amphetamine (Glennon 1987). It is prepared by the oxidation of phenylpropanolamine (Parke 1957).



2,5-Dimethoxy-cathanone

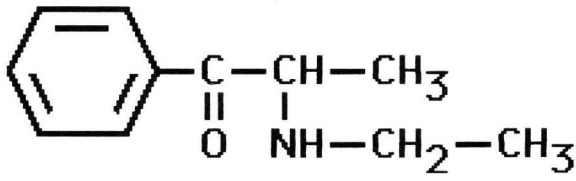
2,5-Dimethoxy-cathinone is a peripheral blood-vessel contractor (Morishita 1961).



Methcathinone

2-Methamino-1-phenyl-propanone (ephedrone) is a molecule that has not been tested in human subjects, but appears to be a psychostimulant in animal testing. Ephedrone is a homolog of 2-(dimethylamino)propiophenone.

References: (Goldstone 1993) (Young 1993) (Zingel 1991)



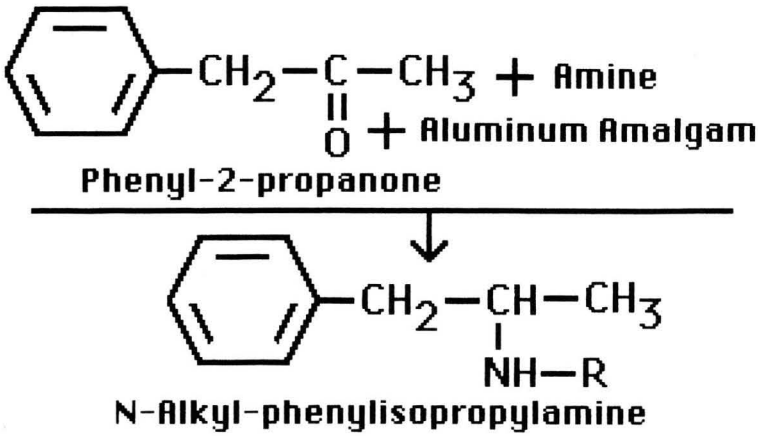
Ethcathinone

No neurotoxic studies have been conducted on either methcathinone or ethcathinone molecules. They might be a safe replacement for the neurotoxic amphetamines used in the conventional treatment of hyperkinetic children, narcoleptics, and the obese.

CHAPTER 8: REDUCTIONS

Reductions (also called hydrogenations) can be very dangerous. Many a skilled chemist have been injured in explosions resulting from the use of powerful reducing agents. Explosions resulting from reductions usually involve the use of, but not limited to, reducing agents such as lithium aluminum hydride, sodium borohydride, etc. The decanted zinc and aluminum amalgam may also be pyrophoric. Hydrogen gas is evolved during reductions. Appropriate precautions must be taken (e.g. ventilation with a sparkless fan) to avoid explosion as hydrogen gas is flammable.

Reduction of Phenyl-2-propanone Using Aluminum Amalgam and Amine Solution



A mixture of substituted phenyl-2-propanone (0.25 mole), 22 grams of aluminum amalgam and 48 grams of 29 % ammonia solution (strong ammonia water) are refluxed in 200 mL ethanol for 3 hours. The mixture is decanted from the aluminum and concentrated. The residue is dissolved in a minimal amount of ether or acetone, acidified with hydrochloric acid and cooled to precipitate the substituted amphetamine hydrochloride. By replacing the ammonia water with 29 % methylamine will produce the N-methyl derivative; 29 % ethylamine, the N-ethyl homolog.

Starting Molecules: p-Methoxyphenyl-2-propanone & ammonia

Product: p-Methoxyamphetamine Reference: (Fusco 1948)

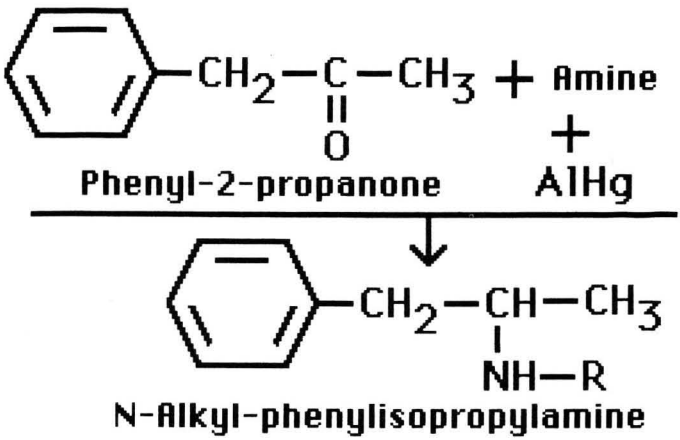
Starting Molecules: p-Methoxyphenyl-2-propanone & methylamine

Product: p-Methoxy-N-methamphetamine Ref.: (Fusco 1948)

Starting Molecules: p-Methoxyphenyl-2-propanone & ethylamine

Product: p-Methoxy-N-ethamphetamine Ref.: (Fusco 1948)

Reduction of P-2-P with Aluminum Turnings, and Mercuric Bichloride with Amine



Phenyl-2-propanone (0.15 mole) is mixed with 100 mL of ethanol, 100 mL of a 25% methylamine solution, 0.15 gram of mercuric bichloride and 20 grams of aluminum turnings. The mixture is refluxed for 2 hours, made alkaline with 60 grams of potassium hydroxide and extracted with approximately 350 mL of ether. The ether solution reduced under reduced pressure and then cooled. A cooled solution of hydrochloric acid is added to precipitate the N-methyl-amphetamine hydrochloride which can be collected by vacuum filtration.

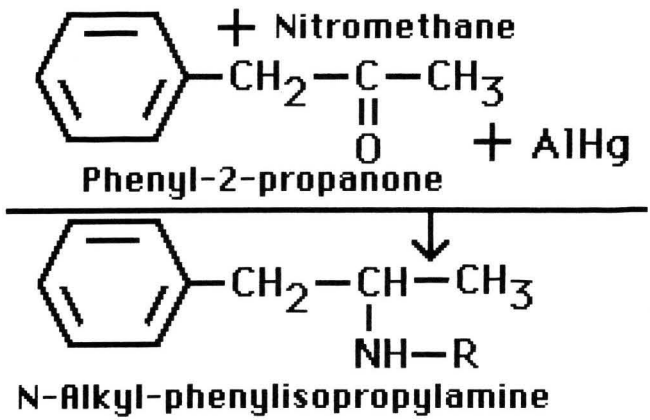
Starting Molecule: Phenyl-2-propanone & methylamine
Pdct.: N-Methylamphetamine Ref.: (Laboratories Amido 1963)

Using Aluminum Foil

Starting Molecule: 1-(1,3-Benzodioxol-5-yl)butan-2-one
& methylamine HCl or methylamine
Product: N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine
Reference : (Nichols 1986)

Starting Molecule: 1-(3,4-Methylenedioxyphenyl)-2-propanone
& methylamine HCl or methylamine
Product: 3,4-Methylenedioxy-N-methylamphetamine
Refs.: (PIHKAL 1991): ethyl-K; methyl-K; Adam; Eden; Eve; MDMC

Reduction Using Aluminum Amalgam with Nitromethane



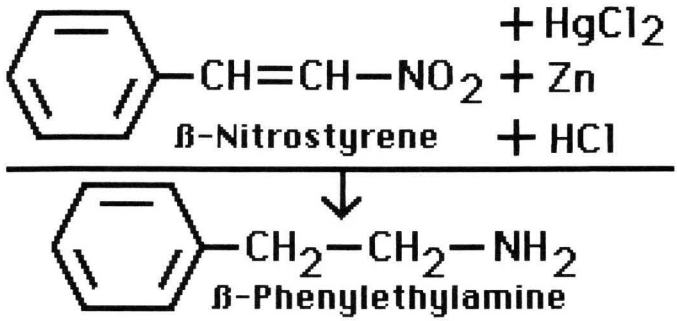
A mixture of substituted phenyl-2-propanone (0.25 moles), nitromethane (25 grams, 0.40 mole) and 150 mL ethanol are added dropwise while stirring to a mixture of 40 grams of aluminum amalgam in 650 mL ethanol. This mixture is refluxed for three hours. The solution is then decanted from the aluminum and concentrated. The residue is dissolved in a minimum quantity of ether or acetone, acidified

with hydrochloric acid and cooled to crystallize the substituted N-alkylamphetamine. The amphetamine salt is collected by suction filtration. The product is washed with ether or acetone. Approximate yield is 0.21 moles of substituted N-alkylamphetamine. By replacing the nitromethane with equal molar quantities of nitroethane (30 grams, 0.40 mole) should produce the N-ethylamphetamine.

Starting Molecules: 2-Methoxyphenyl-2-propanone & nitromethane

Pdct.: 2-Methoxy-N-methylamphetamine Ref.: (Tanaka 1957)

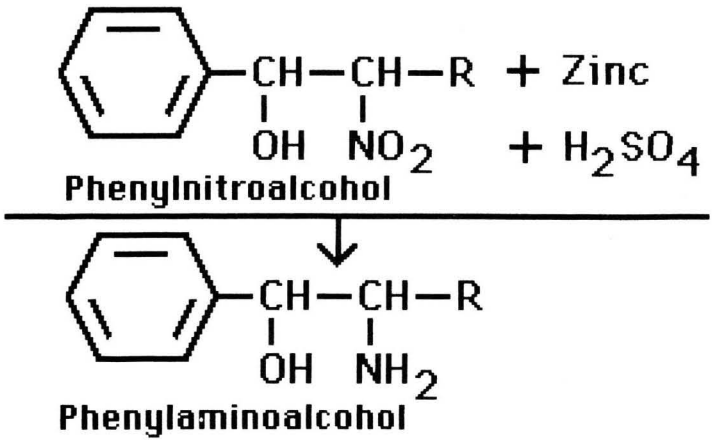
Phenylethylamines from ß-Nitrostyrene, Zinc and Mercuric Bichloride



0.1 Mole of ß-nitrostyrene is mixed in a solution of 500 mL of ethanol containing 100 grams of powdered zinc and 10 grams of mercuric bichloride. The mixture is stirred rapidly as concentrated hydrochloric acid is added until the yellow tinge disappears from the solution. The reaction mixture is rapidly stirred for one half hour following the color disappearance. The solution is filtered to remove excess zinc amalgam. The ethanol is then evaporated to leave a residue of the phenylalkylamine hydrochloride and impurities. The residue is made alkaline with ammonium hydroxide and extracted with ether or appropriate water insoluble solvent. The extract is cooled and cold hydrochloric acid is added to precipitate the phenylethylamine hydrochloride.

Starting Molecule: 3-Bromo-4,5-methylenedioxy-ß-nitrostyrene
Product: 3-Bromo-4,5-methylenedioxy-ß-phenylethylamine
Reference: (Tomita 1968)

Reduction of Phenylnitroalcohols With Use of Zinc



Immediate Precursor	R	Product
Phenyl-2-nitroethanol	H	Phenylethanolamine
Phenyl-2-nitropropanol	CH_3	Phenylpropanolamine

Substituted phenylnitroalcohol (0.25 mole) is dissolved in 85 mL of 95 % ethanol, and 120 grams of zinc dust or pellets (80 to 20 mesh) is added while stirring. Sulfuric acid (340 grams, 30 % acid) is added dropwise with continued stirring. The acid is added at a rate in which the temperature remains between 40 to 45 degrees. (Dehydration occurs with increased temperature). Approximately 12 hours are required. The mixture is stirred for a couple of hours after the addition of the acid. The solution is decanted from the zinc, made very alkaline with an excess of 50 % aqueous sodium hydroxide solution and extracted with approximately 500 mL ether or

appropriate solvent. Hydrochloric or sulfuric acid is added to make the solution acidic and is cooled or concentrated and cooled to precipitate the aminoalcohol salt which is then collected by suction filtration. 0.15 Moles to 0.20 moles of the phenyl-2-aminopropanol (or other amine depending on immediate precursor used) are obtained (yield 60-75 %).

Starting Molecule: 2-Methyl-2-nitro-1-phenyl-1-propanol
Product: 2-Amino-2-methyl-1-phenyl-1-propanol (ephedrine)
Reference: (Bruce 1952) (Nagai 1929)

Starting Molecule: 2-Nitro-1-phenyl-1-propanol
Product: dl-Norephedrine & dl-norpseudo-ephedrine
Refs.: (Hoover 1947) (Kanao 1928) (Nagai 1929; Fe + H_2SO_4)

Starting Molecule: 3,4-Diacetoxyphenylnitroethanol
Pdct.:1-(3,4-Diacetoxyphenyl)-2-aminoethanol Ref.: (Kanao 1929)

Starting Molecule: 1-(3,4-Diacetoxyphenyl)-2-nitropropanol
Pt.:1-(3,4-Diacetoxyphenyl)-2-aminopropanol Ref.:(Kanao 1929)

Aluminum Amalgam

Aluminum amalgam is a commonly used reducing agent because of its availability, low cost and ease of preparation. It can be produced on location which alleviates the hazard of storing the reducing agent.

Keep in mind that the decanted aluminum amalgam may be pyrophoric!

Preparation of Aluminum Amalgam

20 grams of aluminum foil are sliced into 0.5 x 0.5 inch squares and washed with naphtha (lighter fluid) to degrease the metal. The metal is then covered with 2 % sodium hydroxide solution. When the hydrogen evolution sets in, the solution is decanted from the metal, washed quickly and repeatedly with water. 150 mL of a 0.5 % solution of mercuric bichloride is poured on the metal and allowed to sit for 2 minutes. At this time the metal is quickly washed several times with water and 95 % alcohol.

References: Augustine (1968) in Reductions
Journal of Organic Chemistry (1946) 11: 823

Preparation of Mercury Bichloride

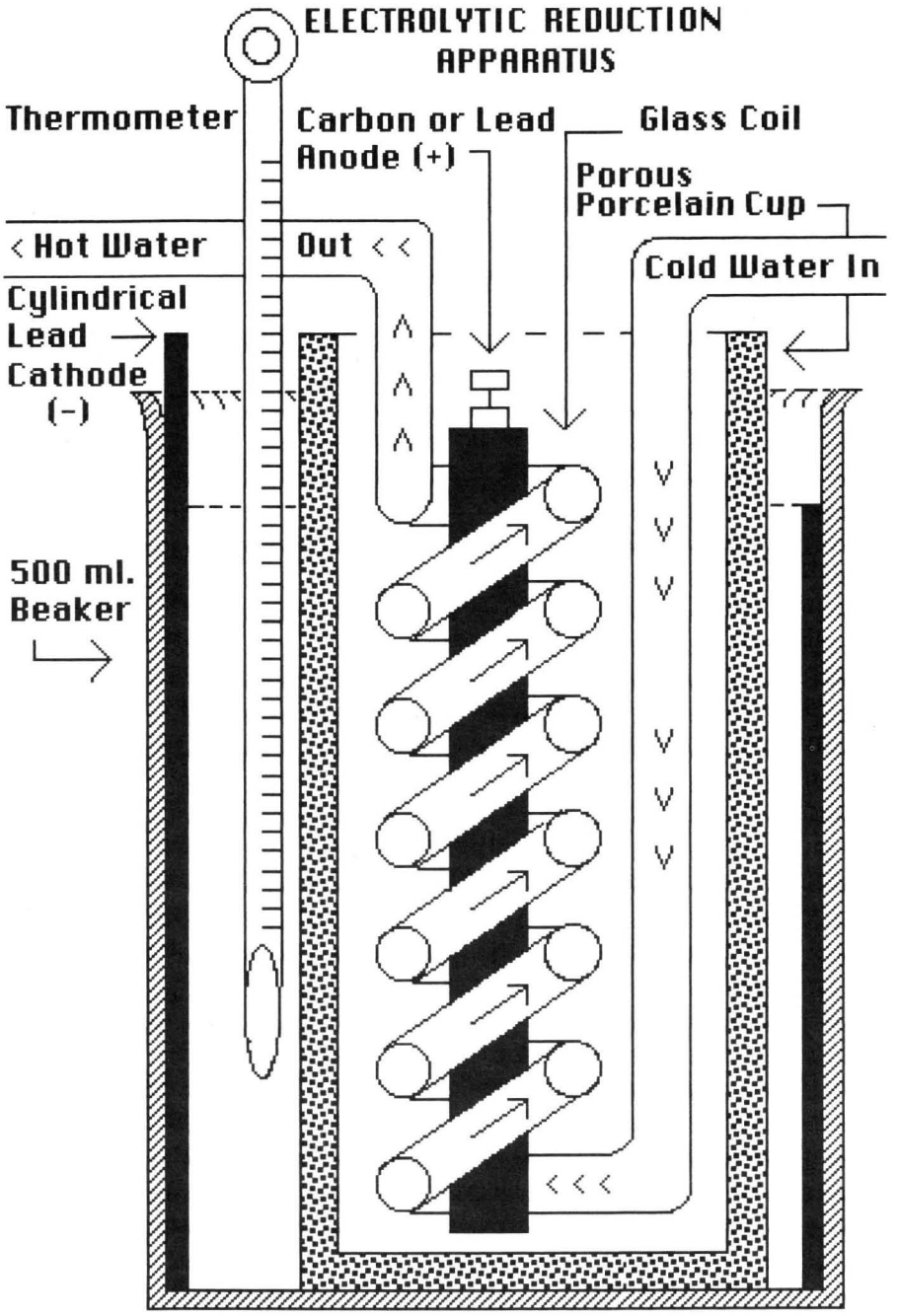
Mercury bichloride can be prepared by several different reactions.

Caution: mercury containing chemicals are poisonous!

A mixture of 12 grams of mercury are boiled with 18 grams of sulfuric acid on a sand bath until a dry white residue remains. This white residue is mercury sulfate. The residue of mercury sulfate is ground with 9 grams of sodium chloride (salt) in an earthenware mortar. The powder is then placed in a sublimation apparatus. A vacuum is drawn on the apparatus and the stopcock is closed to keep the vacuum. The sublimation apparatus is gradually heated to sublime the mixture which condenses mercury bichloride on the walls of the apparatus.

Mercury bichloride can also be produced by dissolving mercuric oxide (red) in hydrochloric acid and evaporating the solution to leave a residue of mercury bichloride.

Mercury bichloride can also be produced by the direct reaction of chloride gas with mercury vapor.


ELECTROLYTIC REDUCTION
APPARATUS
Thermometer
Carbon or Lead
Anode (+)
Glass Coil
Porous
Porcelain Cup
Hot Water
Out
Cold Water In
Cylindrical
Lead
Cathode
(-)
500 ml.
Beaker

ELECTROLYTIC REDUCTION; APPARATUS COMPONENTS

Electrolytic reductions elevate the need to use hazardous reducing agents, metals etc. Electricity is used instead. The following small apparatus suits the needs of most amateur as well as professional chemists. It does not require much space and can be disassembled and stored when not in use. Electrolytic reductions are used to produce amines, alcohols, aldehydes etc.

The electrolytic reduction apparatus has several components. All of these components can be purchased readily or made with locally obtained materials. I will list the various components:

1) The porous porcelain cylindrical cell.

It is composed of unglazed cylindrical porous porcelain cup with the approximate external dimensions of 3 x 6.6 inches. It can be purchased from a laboratory supply company or made at a local ceramics shop. A filtros plate or thin corkpine wood sealed by the use of paraffin may also be used. Porous porcelain cells are commonly used in chemistry class battery experiments.

"An inexpensive substitute for these cups may be made as follows: Wet a sheet of paper, wrap it several times about a large test-tube, folding in to close the bottom. Mold the paper into shape, then coat it, inside and out, with a hot solution made by dissolving 75 grams of gelatin and 100 g. $K_4Fe(CN)_6$ in one liter of water. When the cup has drained and cooled, it may be removed, and inverted until dry."
From: Exercises in General Chemistry (1924)

2) The glass coil.

The reason for the glass coil is to lower the heat from the reduction mixture. It can be made. I would suggest learning how to work with glass as in the chemistry laboratory it saves a lot of money (repairing breaks). The coils are available from laboratory supply companies or can be manufactured to specifications at glass work shops. The glass coils surround the anode and fit with in the porous porcelain cell (the anode chamber).

3) The anode (+).

It is usually composed of lead, carbon, or platinum. Carbon rods can be purchased in art supply stores.

4) The cathode (-).

It is usually composed of lead, mercury or platinum. In this apparatus, the cathode is a piece of lead flashing which is bent to surround the porous porcelain cup and fit within a 500 mL beaker. The lead cathode should have the approximate dimensions of 8.5 x 3.5 x 3/32 inches. A strip of lead is extended upward from the lead sheet for attachment to the negative pole of the power source.

5) A 500 mL beaker is used to hold the apparatus.

6) The DC power supply.

The power supply must produce 12 volts DC at 6 amps. Variations of these currents will produce variable yields. Battery chargers can not be used as a power source. There is no resistance in the reduction apparatus and will over load the battery charger. The current of electricity must be constant. A battery charger will not do this. Battery chargers usually produce a large current in the beginning of charging a battery and tapper off as the battery stores charge and builds resistance. The power supply for the apparatus is available from electronics supply houses. Alligator clips are wired to the output wires so that they can be easily attached to the anode and cathode.

7) A thermometer.

8) A small water circulator.

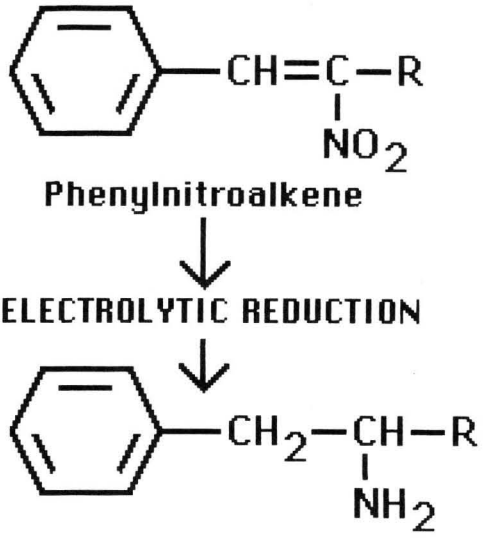
This is used to circulate the water through the glass coils. A circulator will not waste tap water and run up the water bill. These circulators are used to circulate water in small water fountains and can be purchased in any place that supplies lawn ornaments such as garden centers etc.

9) A large container for the reduction apparatus.

The reduction apparatus is placed in a large glass bowl which holds ice and the water circulator. The cold water is circulated through the glass coils and back into the bowl of ice.

References: (Ingersoll; Organic Syntheses Col 1: Organic Syntheses 9) (McMillan 1949) (Norris 1925) (Slotta 1933)

THE ELECTROLYTIC REDUCTION



Immediate Precursor	R	Product
ß-Nitrostyrene	H	Phenylethylamine
Phenyl-2-nitropropene	CH_3	Amphetamine

Low temperature reduction of 1-(phenyl)-1-acetoxy-2-nitropropane will produce d,l-norephedrine (racemic phenylpropanolamine) and also racemic kathine (d,l-norpseudoephedrine).

This apparatus will work equally well with trimethoxy, ethoxy and various other substitutes. Hydroxy groups should be protected (OH groups should be methylated or acetylated) as they may also be reduced. The addition of an excess molar equivalent of formaldehyde into the catholyte compartment, pre-reduction, will N-methylate the amine (Kanao 1929). The addition of acetaldehyde should result in the N-ethylation of the amine.

The cathode compartment contains a solution of 0.13 mole of substituted phenylnitroalkene in 100 mL of glacial acetic acid and 100 mL of absolute alcohol which contains 50 mL of concentrated hydrochloric acid.

The anode compartment is filled to the same level as the cathode liquor with a solution of 14 % hydrochloric acid.

The alligator clips from the power source are connected to the appropriate electrodes, the water is circulated through the coils and the power is turned on. The catholyte is held at 20 degrees for the first six hours and then allowed to rise to 40 degrees for the last six hours. The reduction takes approximately 12 hours. Reduction is usually complete when the catholyte liquor looses its yellow tint.

The catholyte liquor is filtered and poured into 300 mL of water. The unreduced nitroalkene is extracted with ethyl acetate or any other appropriate solvent that the amine hydrochloride is not soluble in (e.g. acetone, ether).

The crude amine hydrochloride, remains in the water solution. The water can be distilled off to leave a mush of the crude amine salt, traces of hydrochloric acid, water and impurities. This mush must be dried of water by use of anhydrous Epson salt (magnesium sulfate) or calcium chloride.

Drying agent: Epson salt or calcium chloride is placed in a Pyrex dish and heated in the oven at 120 degrees C. The Epsom salt will become anhydrous (loose the extra H_2O that is attached to the molecule). It takes on a white very hard constancy. Take the dish of drying agent out of the oven with oven gloves (so as not to get burned). Break up the anhydrous Epsom salt and store in a air tight bottle so as not to absorb atmospheric moisture.

Starting Molecule: dl-threo-1-(Acetoxy-phenyl)-2-nitropropane
Product: dl-Norpseudoephedrine
Reference: (Drefahl 1958)

Starting Molecule: Cinnamic acid
Product: Hydrocinnamic acid
Reference: (Norris 1925) (Ingersoll Organic Syntheses Coll. 1; Organic Syntheses 9)

Starting Molecule: 2,4-Dimethoxy-ß-methylcinnamic acid
Product: 2,4-Dimethoxy-ß-methylhydrocinnamic acid
References: (Woodruff 1942; Ingersoll Organic Syntheses Coll. 1)

Starting Molecule: 2,5-Dimethoxy-ß-methylcinnamic acid
Product: 2,5-Dimethoxy-ß-methylhydrocinnamic acid
References: (Woodruff 1942; Ingersoll Organic Syntheses Coll. 1)

Starting Molecule: 2,5-Dimethoxy-ß-nitrostyrene
Product: 2,5-Dimethoxyphenylethylamine
Reference: (Leaf 1948)

Starting Molecule: 3-Methoxy-4-ethoxy-ß-nitrostyrene
Product: 3-Methoxy-4-ethoxy-phenylethylamine
Reference: (Kondo 1928)

S.M.: 2-(alpha-Methoxy-4-nitropropyl)-4,5-methylenedioxytoluene
Product:ß-Methoxy-ß-(3,4-methylenedioxy-6-methyl)-amphetamine
Reference: (Sugasawa 1954)

Starting Molecule: 6-Methyl-ß-nitroisosafrole
Product: 6-Methyl-3,4-methylenedioxy-amphetamine
Reference: (Sugasawa 1954)

Starting Molecule: ß-Nitro-asarone
Product: 2,4,5-Trimethoxyamphetamine
Reference: (Bruckner 1933)

Starting Molecule: 2-Nitro-1-butanol
Product: 2-Amino-1-butanol Reference: (McMillan 1949)

Starting Molecule: 2-Nitro-2-ethyl-1,3-propandiol
Product: 2-Amino-2-ethyl-1,3-propandiol
Reference: (McMillan 1949)

Starting Molecule: ß-Nitroisosafrole
1-(3,4-Methylenedioxyphenyl)-2-nitropropene-1
Product: 3,4-Methylenedioxy-amphetamine
Reference: (Dal Cason 1990)

Starting Molecule: 2-Nitro-2-methyl-1,3-propandiol
Product: 2-Amino-2-methyl-1,3-propandiol
Reference: (McMillan 1949)

Starting Molecule: 2-Nitro-2-methyl-1-propanol
Product: 2-Amino-2-methyl-1-propanol
Reference: (McMillan 1949)

Starting Molecule: Phenyl-nitropropylene;
1-(Phenyl)-2-nitropropene-1
Product: Amphetamine
Reference: (Alles 1932)

Starting Molecule: PhCOCOMe
Product: Ephedrine
Reference: (Sugino 1953)

Starting Molecule: Salicylic acid
Product: Salicylaldehyde
References: (Balakrishnan 1970) (Dey 1953) (May 1950)
(Tesh 1924) (Udupa 1961)

Starting Molecule: 3,4,5-Timethoxy-ß-nitrostyrene
Product: Mescaline (3,4,5-Trimethoxyphenylethylamine)
Reference: (Slotta 1933)

Drying of The Phenylalkylamine Hydrochloride (a salt)

Sprinkle the anhydrous drying agent on the bottom of a large Pyrex dish. Place the 'wet' phenylalkylamine hydrochloride in a smaller dish, set it in the large dish on the anhydrous Epsom salt and place a cover on the large dish. The moisture from the phenylalkylamine salt will be absorbed by the anhydrous drying agent much like an open box of bicarbonate of soda absorbs the odors in the refrigerator. Allow to stand till the weight of the dish containing the phenylalkylamine hydrochloride remains constant.

Purification And Precipitation of The Substituted Phenylalkylamine Salt

The amine salt is placed in a beaker. A minimal quantity of hot acetone or ether are added. Just enough to dissolve the amine salt. Ether or acetone (or appropriate solvent which the amine salt is insoluble) is used. Cover the solution so as not to absorb moisture and cool in a refrigerator. The amine salt precipitates from the solution and is then filtered from the solvent by vacuum filtration using a water aspirator. The amine salt is again dried with anhydrous drying material and stored in an air tight container.

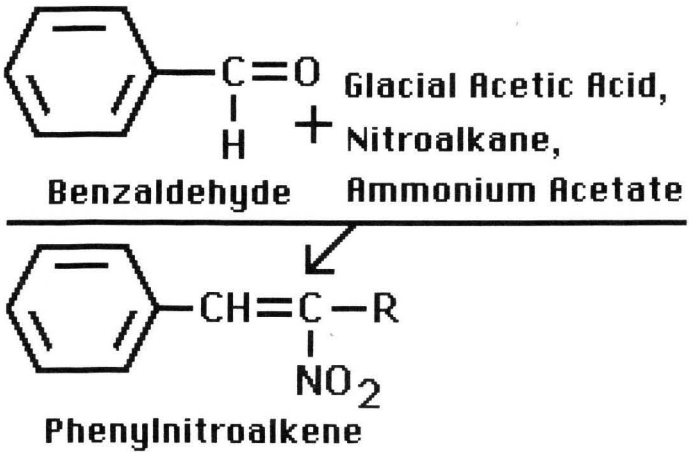
Purification of The Crude Phenylalkylamine Hydrochloride Salt From The Catholyte Liquor

Another purification can be done. To the crude amine salt solution (catholyte liquor), that has been purified of the phenylnitroalkene with solvent washing, 100 grams of concentrated sodium hydroxide solution is added to basify the amine salt and make it soluble in acetone, ether etc. The base amine is then extracted from the sodium hydroxide solution with ether or acetone, concentrate the solution and cool. Hydrochloric acid is added to the cooled solution to precipitate the purified amine hydrochloride salt. Vacuum filter and dry.

This reduction produces 75 % theoretical yields or better of purified amine salt.

CHAPTER 9: PHENYL-2-NITROPROPENE PREPARATION

Phenylnitroalkenes From Benzaldehydes & Nitroalkanes



Nitroalkane	Product
Nitromethane	ß-Nitrostyrene (R = H)
Nitroethane	Phenyl-2-nitropropene (R = CH_3)
1-Nitropropane	Phenyl-2-nitro-1-butene (R = CH_2CH_3)

50 Grams of the substituted benzaldehyde is mixed with 50 mL of nitroalkane, 20 grams of ammonium acetate and 200 mL of glacial acetic acid. A Dean & Stark moisture receiver is attached to the reflux apparatus. The solution is heated on a boiling water bath for three hours and then poured into ice-water. The product will precipitate as an oil or as a solid. Solid precipitates may be collected by vacuum filtration. The oils may be extracted by washing the solution with ether (or any water insoluble solvent). The oils are then obtained by distillation or evaporation of the solvent-phenylnitroalkene solution.

The phenylnitroalkene is purified by recrystallization. Phenylnitroalkene is dissolved in a minimum quantity of ethanol, methanol or acetic acid and then cooled to crystallize the product (this may take several hours in the refrigerator or freezer). Some products may not crystallize and will remain as oils.

Yields are approximately 75 % plus.

Starting Molecules: Benzaldehyde & nitroethane
Pdct.: 1-Phenyl-2-nitropropene Refs.: (Hass 1950; Gairaud 1952)

Starting Molecules: Benzaldehyde & nitropropane
Product: 1-Phenyl-2-nitro-1-butene Reference: (Hass 1950)

Starting Molecules: 4-Bromo-2,5-dimethoxybenzaldehyde & nitroethane
Product: 1-(4-Bromo-2,5-dimethoxyphenyl)-2-nitropropene-1
References: (Barfknecht, 1970; 1971) (Nichols 1970)

Starting Molecules: 2-Bromo-4,5-dimethoxybenzaldehyde & nitroethane
Product: 1-(2-Bromo-4,5-dimethoxyphenyl)-2-nitropropene-1
References: (Barfknecht 1970) (Sepulveda 1972)

Starting Molecules: 4-Bromo-3,5-dimethoxybenzaldehyde & nitroethane
Product: 1-(4-Bromo-3,5-dimethoxyphenyl)-2-nitropropene-1
References: (Barfknecht 1971) (Sepulveda 1972)

Starting Molecules: 5-Bromo-2,4-dimethoxybenzaldehyde & nitroethane
Product: 1-(5-Bromo-2,4-dimethoxyphenyl)-2-nitropropene-1
Reference: (Sepulveda 1972)

Starting Molecules: 2-Bromo-5-methoxybenzaldehyde & nitroethane
Product: 1-(2-Bromo-5-methoxyphenyl)-2-nitropropene-1
Reference: (Barfknecht 1970)

Starting Mols.: 3-Bromo-5-methoxybenzaldehyde & nitroethane
Product: 1-(3-Bromo-5-methoxyphenyl)-2-nitropropene-1
Reference: (Barfknecht 1970)

Starting Mols.: 4-Bromo-3-methoxybenzaldehyde & nitroethane
Product: 1-(4-Bromo-3-methoxyphenyl)-2-nitropropene-1
Reference: (Barfknecht 1970)

Starting Molecules: 2-Bromo-4,5-methylenedioxybenzaldehyde & nitroethane
Product: 1-(2-Bromo-4,5-methylenedioxyphenyl)-2-nitropropene-1
Reference: (Sepulveda 1972)

Starting Molecules: 2,5-Dimethoxybenzaldehyde & nitroethane
Product: 1-(2,5-Dimethoxyphenyl)-2-nitropropene-1
References: (Coutts 1973) (Bollinger 1962) (Merck & Co. 1962)

Starting Molecules: 2,4-Dimethoxybenzaldehyde & nitromethane
Product: 2,4-Dimethoxy-ß-nitrostyrene
References:(Kondo 1928) (Gairaud 1952)

Starting Molecules: 3,4-Dimethoxybenzaldehyde & nitroethane
Product: 1-(3,4-Dimethoxyphenyl)-2-nitropropene-1
Reference: (Gairaud 1952)

Starting Molecules: 3,4-Dimethoxybenzaldehyde & nitromethane
Product: 3,4-Dimethoxy-ß-nitrostyrene Ref.: (Gairaud 1952)

Starting Molecules: 2,5-Dimethoxy-4-ethylbenzaldehyde & nitroethane
Product: 1-(2,5-Dimethoxy-4-ethylphenyl)-2-nitropropene-1
Reference: (Nichols 1973)

Starting Mols.: 2,5-Dimethoxy-4-methylbenzaldehyde & 1-nitropropane
Product: 1-(2,5-Dimethoxy-4-methyl-phenyl)-2-nitro-1-butene
Reference: (Standridge 1976)

Starting Molecules: 2,5-Dimethoxy-p-tolualdehyde & nitromethane
Product: 2,5-Dimethoxy-4-methyl-ß-nitrostyrene
Reference: (Ho 1970)

Starting Molecules: 4-Methoxybenzaldehyde & nitromethane
Product: 4-Methoxy-ß-nitrostyrene
References: (Kondo 1928) (Gairaud 1952)

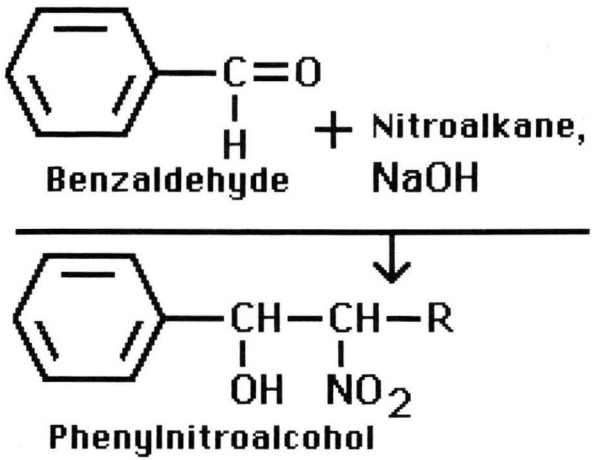
Starting Molecules: 3-Methoxy-4-ethoxybenzaldehyde & nitromethane
Product: 3-Methoxy-4-ethoxy-ß-nitrostyrene
Reference: (Kondo 1928)

Starting Molecules: 2,3,4,5-Tetramethoxybenzaldehyde & nitromethane
Product: 2,3,4,5-Tetramethoxy-ß-nitrostyrene
Reference: (Benington 1955)

Starting Molecules: 2,3,4,6-Tetramethoxybenzaldehyde & nitromethane
Product: 2,3,4,6-Tetramethoxy-ß-nitrostyrene
Reference: (Benington 1955)

Starting Molecules: 2,4,6-Trimethoxy-benzaldehyde & nitromethane
Product: 2,4,6-Trimethoxy-ß-nitrostyrene
Reference: (Benington 1953)

Preparation of Substituted Phenylnitroalcohols



Nitroalkane	Product
Nitromethane	Phenyl-2-nitroethan-1-ol (R = H)
Nitroethane	Phenyl-2-nitropropan-1-ol (R = CH_3)

Method A: The following solution is mixed at 5 degrees. 0.5 Mole of 10 % aqueous sodium hydroxide is vigorous stirred into a mixture of 0.5 mole of benzaldehyde and 2 moles of nitroalkane which has been dissolved in 95 % ethanol. The solution is vigorously stirred for no more than three minutes. The solution is neutralized with 2 % aqueous acetic acid. This halts the reaction and decomposes the sodium derivative of the nitroalcohol. The crude phenylnitroalcohol precipitates out as a yellow or colorless solid or oil. After being allowed to chill in an ice bath for five hours the crude product is collected by vacuum filtration. When the product is an oil, it is extracted by a water insoluble solvent. The solvent is distilled or evaporated to leave the crude oil. Purification is accomplished by recrystallization (if crystallization is possible, oils may not crystallize) in an appropriate solvent.

Method B: 0.5 Mole of substituted benzaldehyde, 0.5 mole of nitroalkane, and 200 mL of 95 % ethanol are mixed and 20 mL of 10 % sodium hydroxide is added while cooling. Four days later, the solution is neutralized with aqueous acetic acid. The ethanol is distilled from the solution. The concentrated solution is cooled to precipitate the crude phenylnitroalcohol. The crude oil or solid phenylnitroalcohol is dissolved in ether (or appropriate water insoluble solvent) and then extracted with sodium bisulfite solution to remove unreacted benzaldehyde. The solvent is washed with water, dried and then distilled to leave the purified substituted phenylnitroalcohol. Yields are approximately 60 %. Yields are practically theoretical if the benzaldehyde is recovered.

Starting Molecules: Anisaldehyde & nitromethane
Product: 1-(p-Methoxyphenyl)-2-nitroethanol
Reference: (Jacob 1951)

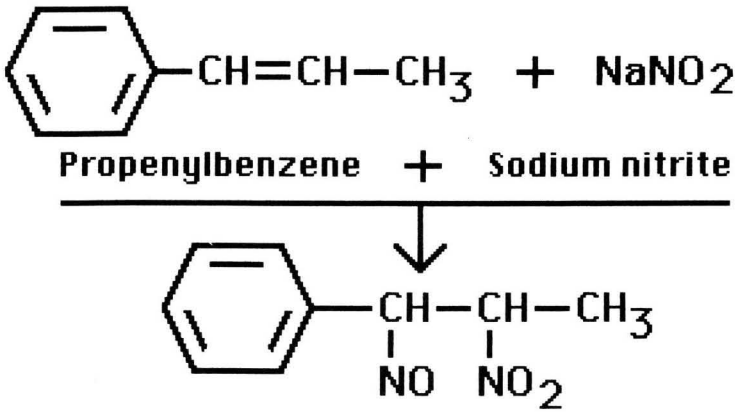
Starting Molecules: Benzaldehyde & nitroethane
Product: 2-Nitro-1-phenyl-1-propanol
References: (Hoover 1947) (Kamlet 1939) (Kanao 1927; 1929) (Nagai 1929) (Vanderbilt 1940)

Starting Molecules: Benzaldehyde & nitroethane & formaldehyde
Product: 2-Methyl-2-nitro-1-phenyl-1-propanol
Reference: (Nagai 1929)

Starting Molecules: p-Ethoxybenzaldehyde & nitromethane
Product: 1-(p-Ethoxyphenyl)-2-nitroethanol
Reference: (Jacob 1951)

Starting Mols.: 3,4,5-Trimethoxybenzaldehyde & nitromethane
Product: 1-(3,4,5-Trimethoxyphenyl)-2-nitroethanol
Reference: (Heacock 1961)

Pseudonitrosites From Substituted Propenylbenzenes



Propenylbenzene pseudonitrosite

Substituted propenylbenzene (0.25 moles) in 280 mL ether is combined with 75 grams of sodium nitrite in 150 mL of water. The mixture is stirred at approximately 0 degrees while 270 mL 20 % sulfuric acid is added dropwise and stirred for one more hour at no higher than 5 degrees. The solution is kept cold to precipitate the pseudonitrosite which is collected by suction filtration. The pseudonitrosite is washed with ether, water and ethanol to give 0.20 to 0.23 moles of propenylbenzene pseudonitrosite.

Starting Molecule: Anethole; 4-Methoxypropenylbenzene
Pdct.:Anethole pseudonitrosite Refs.: (Dessi 1952) (Krámli 1937)

Starting Molecule (Common Name): ß-Asarone
(Chemical Name): 2,4,5-Trimethoxypropenylbenzene
Product: Asarone pseudonitrosite Reference: (Rao 1937)

Starting Molecule: 2,5-Dimethoxypropenylbenzene
Product: 2,5-Dimethoxypropenylbenzene pseudonitrosite
Reference: (Govindachari 1953)

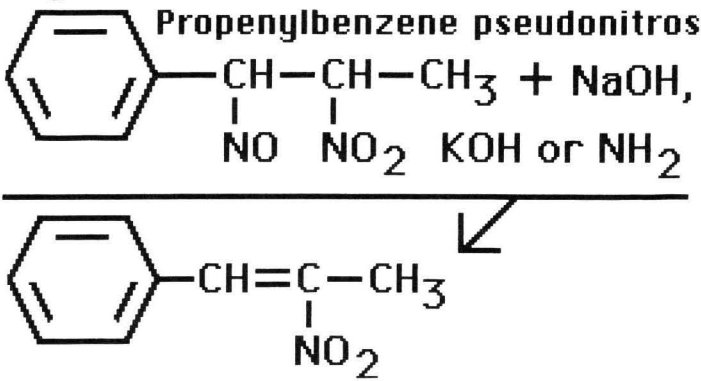
Starting Molecule (Common Name): Isoelemicin
(Chemical Name): 3,4,5-Trimethoxypropenylbenzene
Product: Isoelemicin pseudonitrosite
Reference: (Sugasawa 1937)

Starting Molecule: 2-Methoxypropenylbenzene
Product: 2-Methoxypropenylbenzene pseudonitrosite
Reference: (Horii 1957)

Starting Molecule: 6-Methyl-isosafrole
Product: 6-Methyl-isosafrole pseudonitrosite
Reference: (Sugasawa 1954)

Preparation of Sodium Nitrite: (Cooke 1944) (Morgan 1908) (Pelet) (Shields 1949) (Turner 1915)

Phenyl-2-nitropropenes from Pseudonitrosites



Phenyl-2-nitropropene

Method A: Propenylbenzene pseudonitrosite (0.25 mole) is dissolved in 430 mL of 8 % alcoholic potassium hydroxide by gentle heating (maximum of 25 degrees) and shaking. 1.1 Kilograms of ice is added, acidified with 720 mL of dilute hydrochloric acid and placed in an ice bath for one-half hour. The precipitate is filtered by suction, washed with water, dried in a vacuum desiccator over calcium chloride, giving 0.2 mole of substituted phenyl-2-nitropropene.

The mixture should not be heated at a high temperature because substantial amounts of substituted benzaldehyde will be obtained as a by product. The longer the time of reaction, or at a high temperature will result in more by product being obtained. Example: One mole of pseudonitrosite, at boiling temperature, will produce 0.4 moles of substituted phenyl-2-nitropropene and 0.48 moles of substituted benzaldehyde.This is a very poor yield.

Starting Mol.: 2,4,5-Trimethoxypropenylbenzene pseudonitrosite
Product: 2,4,5-Trimethoxyphenyl-2-nitropropene
Reference: (Bruckner 1933)

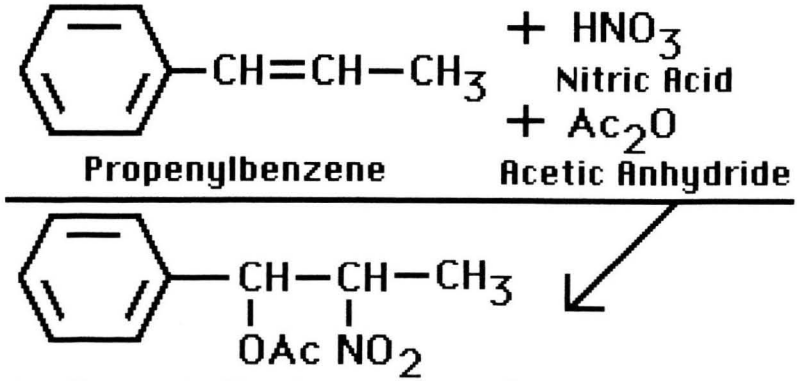
Method B: Substituted propenylbenzene pseudonitrosite (0.25 mole), 430 mL ether and 2.2 liters of 30 % aqueous potassium hydroxide are warmed at 20 degrees for three hours. The ether layer is then concentrated, and the residue recrystallized from alcohol to give 0.20 moles of the substituted phenyl-2-nitropropene.

Starting Molecule: 2-Methoxypropenylbenzene pseudonitrosite
Product: 2-Methoxyphenyl-2-nitropropene Ref.: (Horii 1957)

Method C: Substituted propenylbenzene pseudonitrosite (0.25 mole) is slowly added to a refluxing mixture of 1.5 liters anhydrous ethanol and 150 mL of ammonia saturated ethanol. The mixture is cooled to 0 degrees, and poured into 5.5 liters cold water which precipitates the substituted phenyl-2-nitropropene. The nitropropene is collected by suction filtration, washed with water and dried in a vacuum desiccator over calcium chloride.

Starting Molecule: Anethole pseudonitrosite
Product: ß-Nitro-anethole; 1-(4-Methoxyphenyl)-2-nitropropene-1
Reference: (Dessi 1952)

d,l-threo-1-(Acetoxy-phenyl)-2-nitropropane From Propenylbenzene



d,l-threo-1-(Acetoxy-phenyl)-2-nitropropane

0.5 Mole of substituted propenylbenzene is mixed with 120 mL of acetic anhydride. The solution is stirred at 0 degrees for over 3 hours into 45 mL of 70 % nitric acid containing 180 mL of acetic anhydride. The entire mixture is poured on ice, extracted with ether and distilled to give d,l-threo-1-(acetoxy-phenyl)-2-nitropropane.

Starting Molecule: Anethole
Product: alpha-(4-Methoxyphenyl)-ß-nitropropanol acetate
Reference: (Kramli 1937)

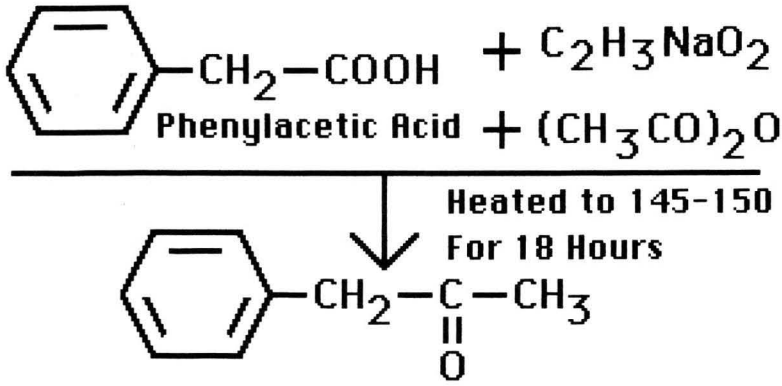
Starting Molecule: 2-Methoxypropenylbenzene
Product: alpha-(2-Methoxyphenyl)-ß-nitropropanol acetate
Reference: (Horii 1957)

Starting Molecule: Propenylbenzene
Product: dl-threo-1-(Acetoxy-phenyl)-2-nitropropane
Reference: (Drefahl 1958) (Fodor 1948)

ß-Nitropropenylbenzenes from phenyl-ß-nitropropanol acetate: (Drefahl 1958; Horii 1957; Kramli 1937; Sugasawa 1937; 1957).

CHAPTER 10: PREPARATION OF KETONES:
Phenyl-2-Propanone From Phenylacetic Acid

This is the most popular synthesis of phenyl-2-propanone. The reaction can be used to produce other ketones other than P-2-P, e.g. acetophenone can be produced in similar yields from benzoic acid. The phenyl-2-propanone or other ketones are obtained from the reaction mixture by fractional distillation to remove diketone impurities.



Phenyl-2-Propanone

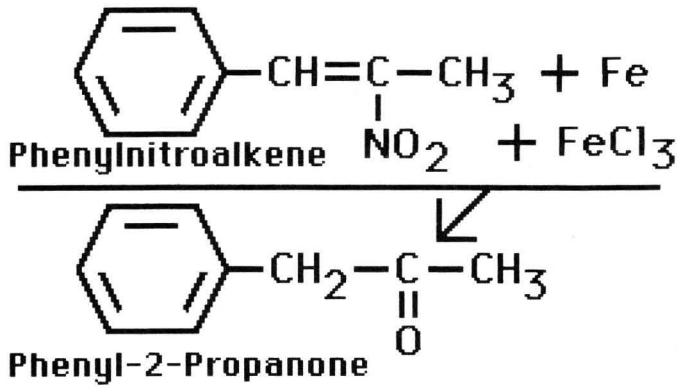
0.5 Mole of phenyl acetic acid is refluxed at 140 to 150 degrees for 18 hours with 115 grams of acetic anhydride and 35 grams of sodium acetate. Approximately 0.4 mole of phenyl-2-propanone can be obtained by fractional distillation. Phenyl-2-propanone distills between 210-215 degrees at atmospheric pressure.

Starting Molecule: Benzoic Acid
Product: Acetophenone
Reference: (chemistry literature)

Starting Molecule: Phenylacetic acid
Product: Phenyl-2-propanone
Reference: (Magidson 1941)

Starting Molecule: p-Methoxyphenylacetic Acid
Product: p-Methoxyphenyl-2-propanone
Reference: (Fusco 1948)

Substituted Phenyl-2-Propanones From Substituted Phenyl-2-Nitropropenes



Phenylnitroalkene

Phenyl-2-Propanone

0.35 Moles of substituted phenyl-2-nitropropene is mixed with 100 mL of toluene. The mixture is stirred and heated to dissolve the phenyl-2-nitropropene. The solution is then vigorously refluxed and stirred while 100 grams of iron powder and 5 grams of ferric chloride (hydrated ferric chloride maybe used) are added. The mixture is refluxed with stirring at 75 degrees. 180 mL of concentrated hydrochloric acid is added over the next two to three hours and heated for another 45 minutes.

The solution is steam distilled until 4 to 5 liters are collected. The steam distillate forms two layers; one aqueous and one non-aqueous (containing: toluene, substituted phenyl-2-propanone and substituted benzaldehyde). The toluene layer is decanted and the aqueous layer is washed with fresh toluene. The toluene layers are combined. The toluene mixture is agitated with 14 grams of sodium bisulfite and filtered to remove aldehydes. The toluene solution is then washed with water to remove sodium bisulfite traces.

The toluene is distilled from the substituted phenyl-2-propanone under reduced pressure (water aspirator) while heating on a steam bath. A yellow liquid of substituted phenyl-2-propanone is left after the distillation of the toluene. Yields are approximately 75 % theoretical.

Start. Mol.: 1-(2,5-Dimethoxy-4-ethylphenyl)-2-nitropropene
Product: 1-(2,5-Dimethoxy-4-ethylphenyl)-2-propanone
Reference: (Nichols 1973)

Start. Mol.: 1-(2,5-Dimethoxy-4-methyl-phenyl)-2-nitro-1-butene
Product: 1-(2,5-Dimethoxy-4-phenyl)-2-butanone
Reference: (Standridge 1976)

Starting Molecule: 1-(2,5-Dimethoxyphenyl)-2-nitropropene-1
Product: 1-(2,5-Dimethoxyphenyl)-2-propanone
Reference: (Bollinger 1962)

Starting Molecule: 1-(2-Methoxyphenyl)-2-nitropropene-1
Product: 1-(2-Methoxyphenyl)-2-propanone
Reference: (Heizelman, 1953)

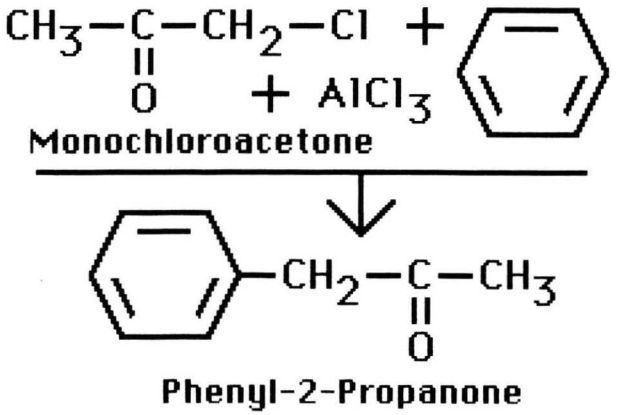
Starting Molecule: 1-(3-Methoxyphenyl)-2-nitropropene-1
Product: 1-(3-Methoxyphenyl)-2-propanone
Reference: (Heizelman, Organic Syntheses)

Start. Mol.: 1-(3-Methoxy-4-hydroxyphenyl)-2-nitropropene-1
Product: 1-(3-Methoxy-4-hydroxyphenyl)-2-propanone
Reference: (Bollinger 1962)
(Pearl 1950)

Starting Molecule: 1-Phenyl-2-nitro-1-butene
Product: 1-Phenyl-2-butanone
Reference: (Hass 1950)

Starting Molecule: 1-Phenyl-2-nitropropene
Product: 1-Phenyl-2-propanone
Reference: (Hass 1950)

Phenyl-2-Propanone From Monochloroacetone



Equipment:

1) A three necked boiling flask.

2) A condenser for reflux. The top of the condenser is attached to an acid trap then vented through a gas absorption bottle and out a window.

3) A separatory funnel for the addition of chloroacetone to the boiling flask.

4) A stirrer with a vapor seal.

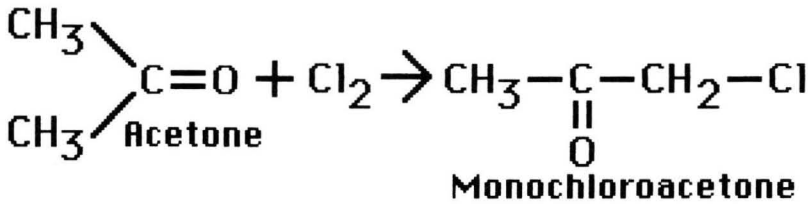
The fumes are highly irritating. The system must be sealed tight and then vented.

165 Grams of anhydrous aluminum chloride is mixed with 420 mL anhydrous benzene. Water is run through the condenser. The stirrer is turned on and the boiling flask is refluxed on an oil bath. 55 Grams (0.6 mole) of chloroacetone is dripped slowly into the reaction flask over a period of two hours. The solution is refluxed for a total of five hours. The solution becomes blackened. The reaction is cooled to room temperature. Water is added through the separatory funnel into the boiling flask, while stirring, until the evolution of hydrogen chloride gas ceases. When the evolution of gas has stopped

90 mL of water and 85 mL of concentrated hydrochloric acid is added. Two layers will form. The benzene layer is decanted from the solution and the aqueous layer is extracted with 500 mL of benzene or toluene. The benzene (or toluene) solutions are combined. The benzene (or toluene) is distilled to leave an oily residue of phenyl-2-propanone and contaminants. The phenyl-2-propanone is fractionally distilled from the residue. The B.P. of phenyl-2-propanone is 216.5 degrees. Yields are 30 % theoretical.

Starting Molecule: Methoxybenzene
Product: p-Methoxy-phenyl-2-propanone
Reference: (Fusco 1948) (Mason 1940)

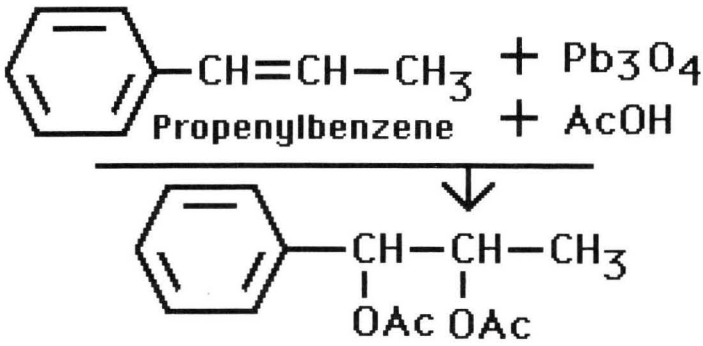
Preparation of Monochloroacetone



50 Grams of acetone is mixed with 50 grams of 5 % hydrochloric acid. The flask is cooled to 10 degrees and 50 grams of chlorine gas is bubbled through the solution (an aquarium aeration stone). The solution is heated at 45 degrees. The oily layer is separated and washed with water and then extracted with ether. The ether extract is dried and then distilled to obtain the impure monochloroacetone. The B.P. of monochloroacetone is 119 degrees. Yields are approximately 80 % theoretical.

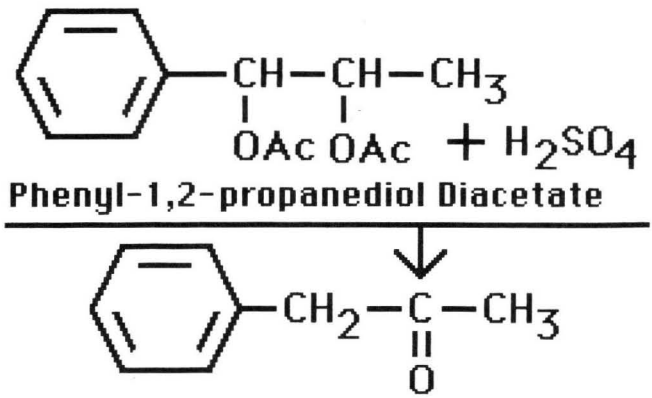
Starting Molecule: Acetone
Product: mono-Chloroacetone Reference: (Okeda 1956)

Phenyl-2-propanones From Propenylbenzenes



Propenylbenzene

Phenyl-1,2-propanediol Diacetate



Phenyl-1,2-propanediol Diacetate

Phenyl-2-Propanone

0.7 Mole of substituted propenylbenzene is mixed with 800 mL of glacial acetic acid. To this solution is added, in proportions, 400 grams of lead tetroxide. This is stirred for one hour at 40 degrees. A small quantity of water is added and the solution is distilled under reduced pressure to leave a residue. The residue is extracted with ether or appropriate solvent and evaporated or distilled under reduced pressure to leave the substituted phenyl-1,2-propanediol diacetate.

Substituted Phenyl-2-Propanones From Substituted Phenyl-1,2-Propanediol Diacetates

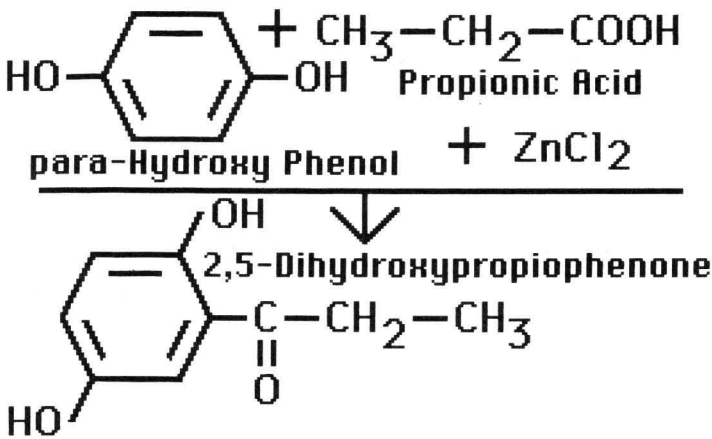
The previous solution containing the substituted phenyl-1,2-propanediol diacetate is mixed with 600 mL of 20% sulfuric acid and refluxed for 3 hours. This solution is then extracted with ether or appropriate solvent. The solvent is distilled under reduced pressure to leave 0.3 moles of the substituted phenyl-2-propanone.

Starting Molecule: 2-Methoxypropenylbenzene
Product: 2-Methoxyphenyl-1,2-propanediol
Reference: (Tanaka 1957). See also (Dal Cason 1984).

Starting Molecule: 2-Methoxy-phenyl-1,2-propanediol diacetate
Product: 2-Methoxyphenyl-2-propanone
Reference: (Tanaka 1957); Also check (Sunagawa 1952)

Starting Molecule: Phenyl-1,2-propanediol
Product: Phenyl-2-propanone
Reference: (Hamada 1950) (Murahashi 1950)

FRIEDEL-CRAFTS REACTION; KETONES FROM PHENOLS



Starting Molecule: Pyrogallol; (2,3-Dihydoxy-phenol)
Reagents: Zinc Chloride, Caproic Acid
Product: 2,3,4-Trihydoxyphenyl-n-Amyl Ketone
Reference: (Hart 1936)

Starting Molecule: Resorcinol; (2-Hydroxy-phenol)
Reagents: Zinc Chloride, Glacial Acetic Acid
Product: 2,4-Dihydroxyacetophenone
Reference: (Cooper 1941)
Further Reference: (Noller 1924)

Methylation of Dihydroxy Ketones:

Starting Molecule: 2,6-Dihydroxyacetophenone
Product: 2,6-Dimethoxyacetophenone
Reference: (Borche 1907)

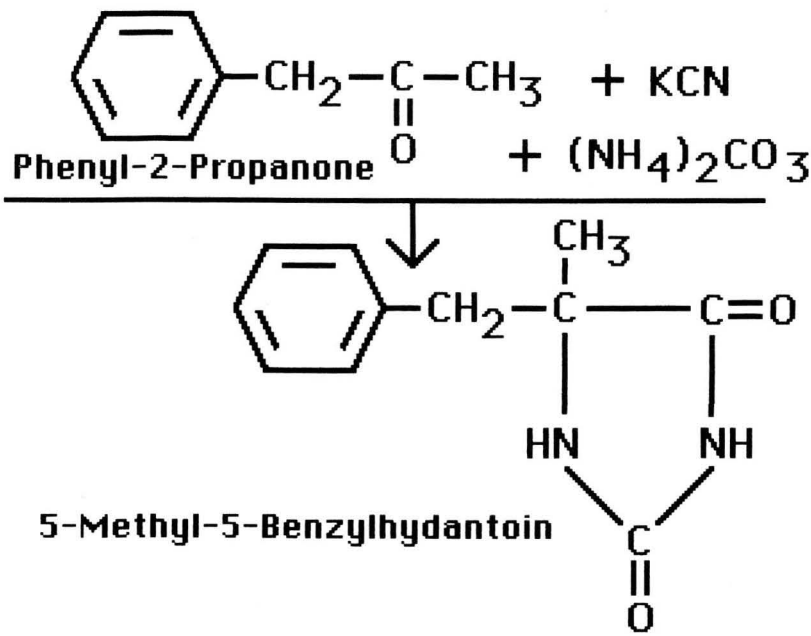
Starting Molecule: 4-O-Benzoylphloracetophenone
Product: 4-O-Benzoyl-2,6-dimethoxyacetophenone
Reference: (Sugasawa 1934)

CHAPTER 11: PREPARATION OF PHENYLALANINES

Preparation of Substituted Alpha-Methyl-Phenylalanines From Phenyl-2-Propanones

Alpha-methyl-phenylalanine, L-tyrosine, and 2,5-dimethoxy-alpha-methyl-phenylalanine have been studied for use as anti-hypertensives. alpha-Methyl-phenylalanine can be decarboxylated to form amphetamine.

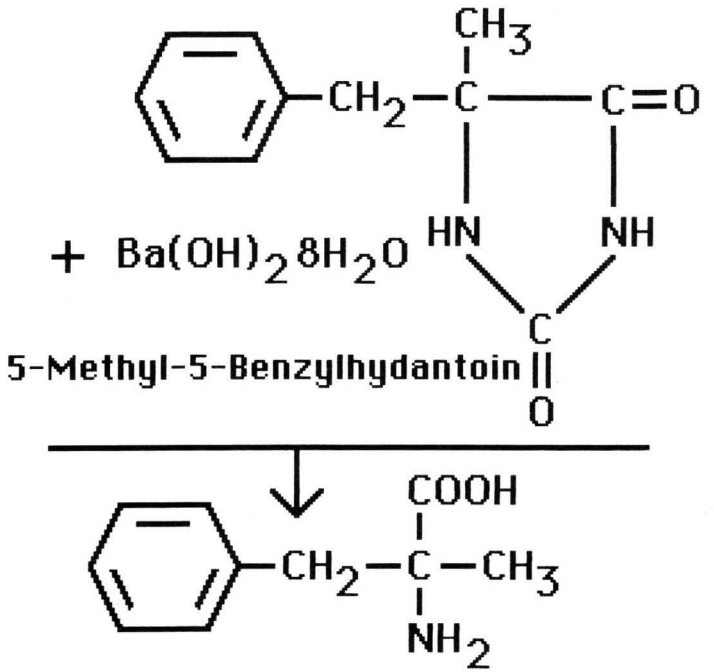
Preparation of 5-Benzyl-5-Methylhydantoin



0.25 Mole of substituted phenyl-2-propanone is mixed with 22 grams of potassium cyanide, 75 grams of ammonium carbonate and 370 mL of 50 % alcohol. The mixture is heated at 67 degrees for seven hours then cooled to precipitate the 5-benzyl-5-methylhydantoin. Yields are 95 % + theoretical.

Caution!: Cyanide chemicals and reaction fumes are deadly toxic. Alkyl nitrite must be within immediate reach in case of hydrogen cyanide gas inhalation.

Preparation of Alpha-Methyl-1-Phenylalanine



Alpha-Methyl-1-Phenylalanine

0.2 Mole of substituted 5-methyl-5-benzylhydantoin is mixed with 300 grams barium hydroxide heptahydrate and 2.9 liters of water. The solution is refluxed for 59 hours with rapid stirring under an inert atmosphere of nitrogen, argon, etc. 1.5 Liters of water is added and the pH is adjusted to 7 (neutral) with 10 % sulfuric acid. The precipitated barium sulfate is filtered from the solution. The filtrate is distilled to dryness under reduced pressure. The residue is dissolved in 1.4 liters anhydrous alcohol and filtered through diatomaceous earth. The alcohol is distilled under reduced pressure to leave the substituted alpha-methyl-phenylalanine. Yields are 90 % + theoretical.

In laboratory studies, pretreatment of animals with alpha-methyl-tyrosine blocks the neurotoxic action of amphetamines. Substituted phenylalanines can be produced from substituted 5-benzylhydantoins.

Starting Molecule: 2,5-Dimethoxyphenyl-2-propanone
Product: 5-Methyl-5-(2,5-dimethoxybenzyl)-hydantoin
Reference: (Bollinger 1962) (Merck 1962)

Starting Molecule: 3,4-Dimethoxyphenyl-2-propanone
Product: 4-Methyl-4-(3´,4´-dimethoxybenzyl)-hydantoin
Reference: (Stein 1955) (Pfister 1959)

Starting Molecule: 3-Methoxyphenyl-2-propanone
Product: 4-Methyl-4-(3´-methoxybenzyl)-hydantoin
Reference: (Stein 1955) (Pfister 1959)

Starting Molecule: Phenyl-2-propanone
Product: 4-Methyl-4-(benzyl)-hydantoin
Reference: (Stein 1955)

Preparation of Alkyl nitrite: (Chretien 1945, 1957) (Rangaswami 1952) (Solovcichik 1955) (Yunker 1960)

Starting Mol.: 4-Methyl-4-(3´,4´-dimethoxybenzyl)-hydantoin
Product: alpha-Methyl-3,4-dimethoxyphenylalanine
Reference: (Stein 1955) (Pfister 1959)

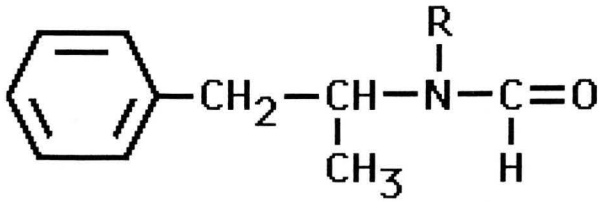
Starting Mol.: 5-Methyl-5-(2,5-dimethoxybenzyl)-hydantoin
Product: alpha-Methyl-2,5-dimethoxyphenylalanine
Reference: (Bollinger 1962) (Merck 1962)

Starting Molecule: 4-Methyl-4-(3´-methoxybenzyl)-hydantoin
Product: alpha-Methyl-3-methoxyphenylalanine
Reference: (Stein 1955) (Pfister 1959)

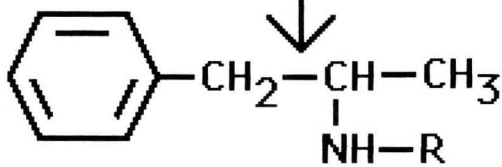
Starting Molecule: 4-Methyl-4-(benzyl)-hydantoin
Product: alpha-Methyl-phenylalanine
Reference: (Stein 1955)

Starting Molecule: 5-Methyl-5-(benzyl)-hydantoin
Product: alpha-Methyl-dl-phenylalanine
Reference: (Potts 1955) (Pfister 1959)

CHAPTER 12:
PREPARATION OF AMPHETAMINES FROM AMIDES
Substituted N-Alkyl-Amphetamine
From Substituted Phenylisopropyl-N-Formamides



1-Phenyl-2-(Formylalkylamino)propane



N-Alkyl-Amphetamine

Method 1:

0.5 Mole of the substituted phenyl-2-(formyl-N-alkylamino)propane is refluxed for 5 hours with 600 mL of 25 % sodium hydroxide. The mixture is steam distilled. The steam distillate containing the N-alkyl amphetamine is extracted with ether or appropriate water insoluble solvent and concentrated. Hydrochloric acid is added to the solvent and chilled to precipitate the substituted phenyisopropyl-N-alkylamine hydrochloride salt which can be suction filtered. Approximately 90 % theoretical yields can be obtained.

Start. Molecule: 1-(2-Chloro-phenyl)-2-(formylamino)propane
Product: 2-Chloro-amphetamine Reference: (Johns 1938)

Starting Molecule: N-(Dimethylbenzylcarbinol)-formamide
Product: Dimethylbenzylcarbinamine (Phentermine)
Reference: (Ritter 1948)

Start. Molecule: 1-(4-Fluoro-phenyl)-2-(formylamino)propane
Product: 4-Fluoro-phenylisopropylamine (4-Fluoro-amphetamine)
Reference: (Suter 1941)

Starting Molecule: N-Methyl-N-formyl-MDA
Product: 3,4,-Methylenedioxy-N-methamphetamine
Reference: (Dal Cason 1990)

Starting Molecule: Phenyl-2-(formylamino)propane
Product: Phenylisopropylamine (Amphetamine)
Reference: (Magidson 1941)

Method 2:

0.5 Mole of phenyl-2-(formyl-N-alkylamino)-propane is refluxed with 150 mL of concentrated hydrochloric acid for one hour. Water may be added to keep the 1-phenyl-2-(formyl-N-alkylamino)propane in solution. The reaction solution is then basified with sodium hydroxide and extracted with benzene or appropriate water insoluble solvent. The solvent is concentrated by distillation, hydrochloric acid is added and the solution is refrigerated to precipitate the amphetamine hydrochloride salt. The product is collected by suction filtration.

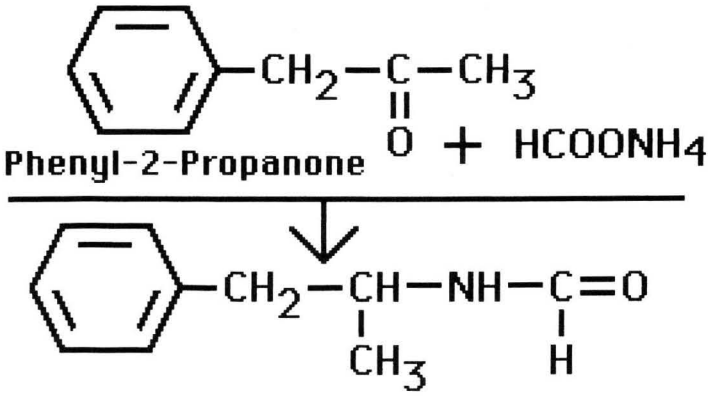
Starting Molecule: N-(Benzylmethylcarbinyl)-acetamide
Product: Methylbenzylcarbinamine (amphetamine)
Reference: (Ritter 1948)

Starting Molecule: N-Methyl-N-formyl-MDA
Product: 3,4,-Methylenedioxy-N-methamphetamine
Reference: (Dal Cason 1990)

Start. Mol.: 1-(2-Methoxyphenyl-2-(formylamino)-propane
Product: 2-Methoxyamphetamine Ref.: (Heizelman, 1953)

Starting Molecule: 1-(Phenyl-2-(formylamino)-propane
Product: Amphetamine Ref.: (Bobranski 1941)

LEUCKART-WALLACH REACTION: Substituted 1-Phenyl-2-(Formylamino)propane From Substituted Phenyl-2-Propanone And Ammonium Formate



Phenyl-2-Propanone

1-Phenyl-2-(Formylamino)propane

The reaction is done in a distillation apparatus. As the boiling flask is heated, a mixture of water and ketone is distilled into the receiving flask. When the water is not simultaneously distilled, the reaction will not occur. During the course of this reaction the original mixture, which is composed of two layers, becomes homogeneous. The ketone is transferred back into the boiling flask.

100 Grams of ammonium formate and 0.5 moles of substituted P-2-P are placed in a boiling flask along with boiling stones (several pieces of porcelain) to prevent bumping. The mixture is heated on a small flame. The contents will melt and form two layers. The mixture begins to distill at 140 degrees. The mixture becomes homogeneous between 150 to 160 degrees. The heating is stopped when the temperature reaches 185 degrees.

The distillate forms two layers. The water insoluble layer is the top layer and contains the substituted phenyl-2-propanone. The upper layer of the distillate is separated from the bottom aqueous layer and is poured back into the boiling flask.

The solution is refluxed for two more hours until the temperature reaches 185 degrees. The solution is then extracted with an appropriate solvent and evaporated to leave the 1-phenyl-2-(formylamino)propane.

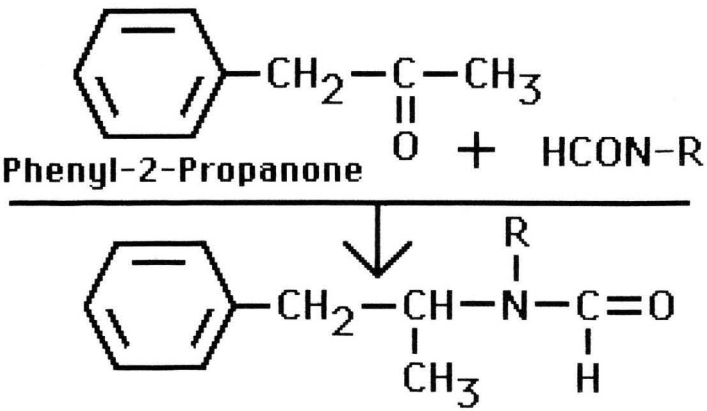
Formamide can be recycled from the aqueous layer of the distillate by distilling to 165 degrees. The formamide can be purified by crystallization or fractional distillation. This is unnecessary as long as the recovered formamide is going to be used with the same ketone in future reactions.
Reference: (Ingersoll 1936)

Starting Molecule: 1-(2-Methoxyphenyl)-2-propanone
Product: 1-(2-Methoxyphenyl)-2-(formylamino)propane
Reference: (Heizelman, 1953)

Starting Molecule: 3,4-Methylenedioxyphenyl-2-propanone
Product: 1-(3,4-Methyledioxyphenyl)-2-(formylamino)propane
References: (Dal Cason 1990) (Elks 1943)

Starting Molecule: Phenyl-2-propanone
Product: Phenyl-2-(formylamino)propane.
References: (Bobranskii 1941)

Substituted 1-Phenyl-2-(Formylalkylamino)propane From Substituted P-2-P And N-Alkylformamide



Phenyl-2-Propanone

1-Phenyl-2-(Formylalkylamino)propane

0.5 Mole of substituted 1-phenyl-2-propanone is refluxed at 180 to 195 degrees for five to nine hours with 2 moles of formamide or N-alkylformamide.

Amide Used	**Product**
Formamide (R = H)	1-phenyl-2-(formylamino)propane

N-alkylformamide	**R**	**Homolog Produced**
N-methylformamide	CH_3	N-methyl homolog
N-ethylformamide	C_2H_5	N-ethyl homolog

The mixture is extracted with chloroform or appropriate solvent. The solvent is distilled to leave the 1-phenyl-2-(formylamino)propane or 1-phenyl-2-(formylalkylamino)-propane.

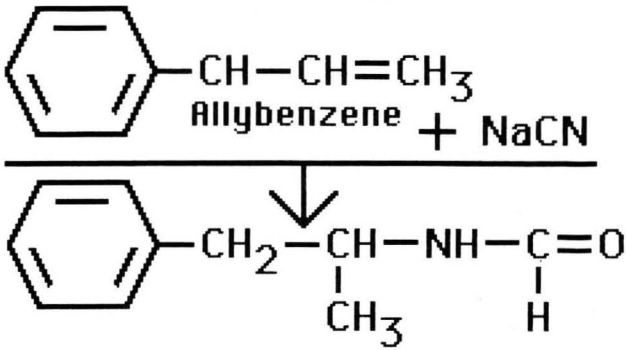
Starting Molecule: 1-(2-Chloro-phenyl)-2-propanone
Product: 1-(2-Chloro-phenyl)-2-(formylamino)propane
Reference: (Johns 1938)

Starting Molecule: 1-(4-Fluoro-phenyl)-2-propanone
Product: 1-(4-Fluoro-phenyl)-2-(formylamino)propane
Reference: (Suter 1941)

Starting Molecule: 1-(3,4-Methylenedioxyphenyl)-2-propanone
Product.: 1-(3,4-Methylenedioxyphenyl-2-(formylamino)propane
Reference: (Dal Cason 1990) (Elks 1943)

Starting Molecule: Phenyl-2-propanone
Product: 1-Phenyl-2-(formylamino)propane
Reference: (Magidson 1941)

RITTER REACTION
Substituted 1-Phenyl-2-(Formylamino)propane From Substituted Allybenzene or Phenyl-2-Propanol And Sodium Cyanide



1-Phenyl-2-(Formylamino)propane

Caution!: Cyanide chemicals and reactions are deadly toxic. Alkyl nitrite must be within immediate reach in case of hydrogen cyanide gas inhalation.

Solution A:

24 Grams of sodium cyanide is stirred into 70 mL of glacial acetic acid with cooling.

Solution B:

A solution of 125 grams of sulfuric acid is mixed with 70 mL of glacial acetic acid.

Solution B is added to solution A with rapid stirring maintaining the temperature at 20 degrees. 0.5 Moles of the substituted phenyl-2-propanol or allybenzene is added rapidly. The temperature spontaneously raises up to 80 degrees. Maintain the temperature at 70 degrees for 30 minutes. The phenyl-2-propanol or allybenzene will dissolve into the solution as this reaction takes place.

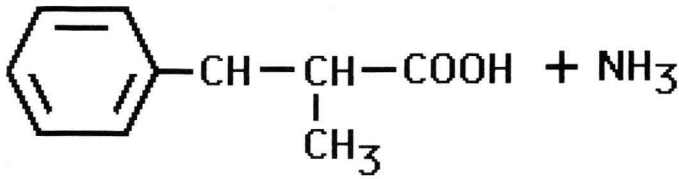
The substituted 1-phenyl-2-(formylamino)propane is precipitated from the solution by adding 750 mL of cold water and neutralizing the pH of the solution with sodium carbonate or sodium hydroxide. The substituted 1-phenyl-2-(formyl-amino)propane precipitates as a yellow to red oil. When this takes place the two layered solution is extracted with ether or appropriate solvent that is water insoluble. The solvent is distilled to leave the substituted 1-phenyl-2-(formylamino)-propane. Yields are 60 % theoretical.

Substituted propenylbenzenes can also be used in this reaction. According to Markovnikov's rule, there should be a 30 % yield of 1-phenyl-2-(formylamino)propane and a 30 % yield of 1-phenyl-1-(formylamino)propane.

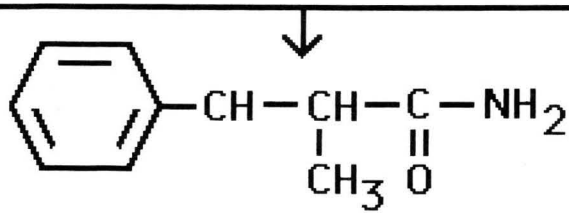
Starting Molecule: Dimethylbenzylcarbinol
Product: N-(Dimethylbenzylcarbinol)-formamide
References: (Bruce 1952) (Ritter 1948)

Starting Molecule: Methallybenzene
Pdct.: N-(Dimethylbenzylcarbinol)-formamide (Ritter 1948)

alpha-Methyl-phenylpropionamide
From alpha-Methyl-phenylpropionic acid



alpha-Methyl-phenylpropionic acid



alpha-Methyl-Phenylpropionamide

alpha-Methyl-phenylpropionic acid is transformed into the ammonium salt. Ammonia is bubbled for 2 hours through the heated (220 degrees) ammonium salt of alpha-methyl-phenylpropionic acid to produce the alpha-methyl-phenylpropionamide. The amide is crystallized in benzene.

Star. Molecule: alpha-Methyl-3,4-dimethoxyphenylpropionic acid
Product: alpha-Methyl-3,4-dimethoxy-phenylpropionamide
Reference: (Ide 1940)

St. Molecule:alpha-Methyl-3,4-methylenedioxyphenylpropionic acid
Product: alpha-Methyl-3,4-methylenedioxyphenylpropionamide
Reference: (Dal Cason 1990) (Ide 1940)

WILLGERODT REACTION
ß-Phenylpropionamide
From Various Starting Molecules

5 Grams of starting molecule is mixed with 13 grams of sulfur, 25 mL of concentrated ammonium hydroxide and 12.5 mL of pyridine and heated at 165 degrees for 4 hours in a thick sealed hard glass bomb tube (not Pyrex). The test tube is then allowed to cool to room temperature. When cooled, the pressure of the tube has also decreased and may be opened. The liquid mixture is evaporated on an evaporating dish heated on a hot water bath. The sulfur and product is extracted from the dried mixture with approximately 100 mL of boiling water. The water is cooled to precipitate the ß-phenylpropionamide. The filtrate can be further concentrated and cooled which precipitates more ß-phenylpropionamide containing traces of phenylacetic acid or hydrocinnamic acid.

Starting Molecule: trans-alpha-Methylcinnamic Acid
Product: ß-Phenylpropionamide
Reference: (Davis 1946)

Starting Molecule: Phenylacetone
Pdct.: ß-Phenylpropionamide Ref.: (Carmack 1946) (King 1946)

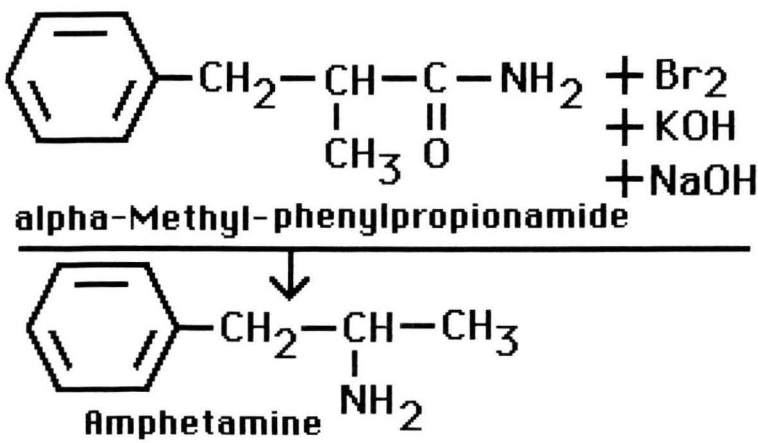
Starting Molecule: ß-Phenylpropionaldehyde
Product: ß-Phenylpropionamide
Reference: (Carmack 1946)

Starting Molecule: 1-Phenylpropene (Propenylbenzene)
Product: ß-Phenylpropionamide
Reference: (Carmack 1946)

Starting Molecule: 1-Phenylpropyne
Product: ß-Phenylpropionamide
Reference: (Carmack 1946)

Starting Molecule: Propiophenone
Product: ß-Phenylpropionamide
Reference: (DeTar 1946)

THE HOFMANN REACTION



Amphetamine from alpha-Methyl-phenylpropionamide

0.5 Mole of amide is mixed into a cooled (below 15 degrees) solution of 43 grams of bromine in 20 moles of 10 % potassium hydroxide. The amide is dissolved by shaking

the solution and then filtered. The filtrate is refluxed at 70 to 80 degrees for 1 $^{1}/_{2}$ hours. 80 Grams of sodium hydroxide is added to the solution and the mixture is heated at 80 degrees for an additional 2 hours. The solution is extracted with ether or appropriate water insoluble solvent to extract the oily amine. The solution is dried and evaporated to reduce the solvent volume and cooled. Hydrochloric acid is added to precipitate the amine hydrochloride.

Starting Molecule: Dimethoxy-ß-methylhydrocinnamide
Product: Dimethoxyphenyl-n-propylamine
Reference: (Woodruff 1942)

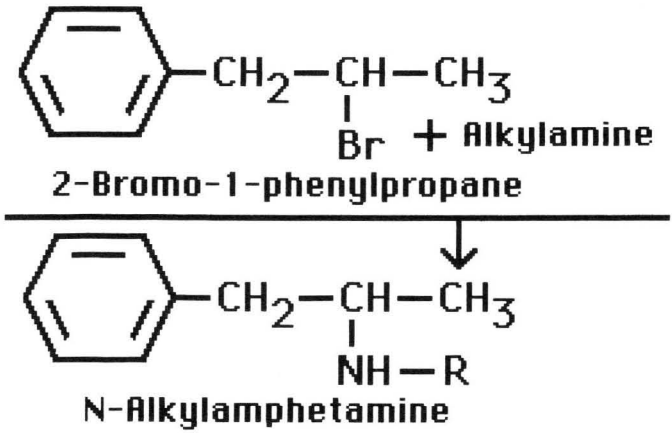
Starting Molecule: alpha-Methyl-2,5-dimethoxyphenylpropionamide
Product: 2,5-Dimethoxyamphetamine
Reference: (Govindachari 1953)

Starting Molecule: alpha-Methyl-dimethoxyphenylpropionamide
Product: Dimethoxyamphetamine
Reference: (Ide 1940)

Starting Molecule: alpha-Methyl-methoxyphenylpropionamide
Product: Methoxyamphetamine
Reference: (Woodruff 1938)

St. Molecule: alpha-Methyl-3,4-Methylendioxyphenylpropionamide
Product: 3,4-Methylenedioxyamphetamine
Reference: (Dal Cason 1990) (Ide 1940)

CHAPTER 13
Amphetamines From alpha Bromo-phenylpropane



A mixture of 0.02 mole of phenyl-2-bromopropane is heated at 130 degrees with a solution of approximately 18 % methylamine solution. The solution is evaporated to leave a residue of methamphetamine. The methamphetamine is then dissolved in a minimal solution of ether or appropriate solvent and cooled to precipitate the crystals of methamphetamine hydrochloride.

Starting Molecule: 3,4-Dimethoxyphenyl-2-bromopropane
Product: 3,4-Dimethoxy-N-methylamphetamine
Reference: (Biniecki 1960)

Starting Molecule: p-Fluorophenethyl Bromide
Reagents: Ammonia
Product: p-Fluorophenylethylamine Ref.: (Suter 1941)

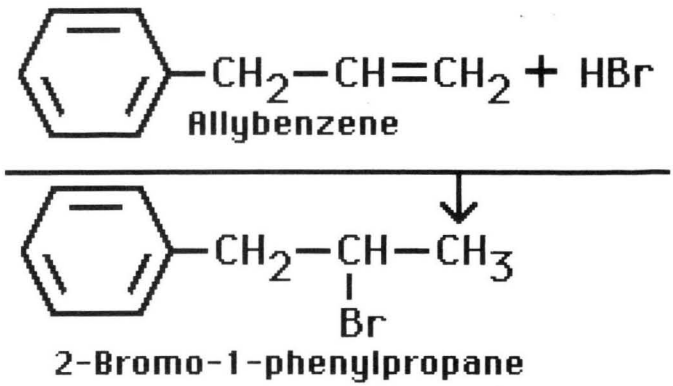
Starting Molecule: p-Fluorophenethyl Bromide
Reagents: Methylamine
Pdct: N-Methyl-p-fluorophenylethylamine Reference: (Suter 1941)

Starting Molecule: 3,4-Methylenedioxyphenyl-2-bromopropane
Reagent: Methylamine
Product: 3,4-Methylenedioxy-N-methylamphetamine
Common Name: (MDMA) Reference: (Biniecki 1960)

Using the Sealed Bomb Method

Starting Molecule: 2-Chloro-1-phenylpropane
Reagents: Ammonia
Product: Amphetamine Reference: (Patrick 1946)

Starting Molecule: 2-Chloro-1-phenylpropane
Reagents: Methylamine
Product: N-Methylamphetamine Reference: (Patrick 1946)



2-Bromo-1-phenylpropane from Allybenzene

At 0 degrees, a 0.06 mole of allybenzene is dropwise added to a solution of 40 grams of a 70 % hydrogen bromide solution. The mixture is continued to be cooled at 0 degrees for a period of approximately 15 hours. The mixture is poured on ice at 0 degrees and then extracted with ether or appropriate solvent. The distillation of the mixture is done under reduced pressure to obtain the 2-bromo-1-phenyl-propane.

Starting Molecule: Allybenzene
Product: ß-Bromopropylbenzene
Reference: (Carter 1935)(Riegel 1946)

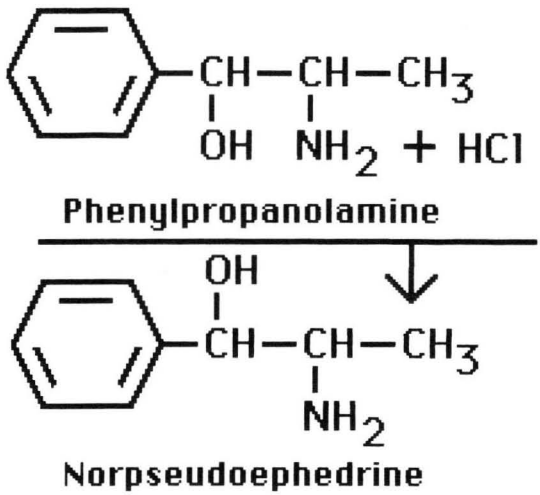
Starting Molecule: 3,4-Dimethoxy-allybenzene
Product: 3,4-Dimethoxyphenyl-2-bromopropane
Reference: (Biniecki 1960)

Starting Molecule: 3,4-Methylenedioxy-allybenzene
Common Name: Safrole
Product: 3,4-Methylenedioxyphenyl-2-bromopropane
Reference: (Biniecki 1960)

CHAPTER 14:
PREPARATION OF NORPSEUDOEPHEDRINE

Preparation of Norpseudoephedrine (Kathine) From Phenylpropanolamine

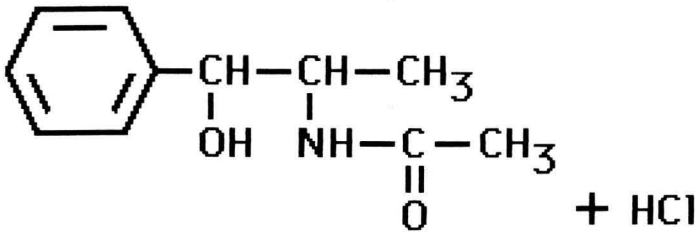
The following reaction is known as an epimerization. It can also be used with ephedrine to produce pseudoephedrine.



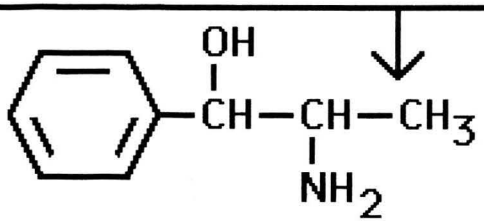
50 Grams of phenylpropanolamine hydrochloride is mixed with 500 mL of 14 % hydrochloric acid. The mixture is refluxed for 12 hours. The solvent is distilled off to leave a residue (49 grams) containing 50 % phenylpropanolamine hydrochloride and 50 % norpseudo-ephedrine hydrochloride.

Reference: (Kanao 1928) (Foder 1948)

Preparation of Norpseudoephedrine (Kathine) From N-Acetyl-Phenylpropanolamine



N-Acetyl-Phenylpropanolamine



Norpseudoephedrine

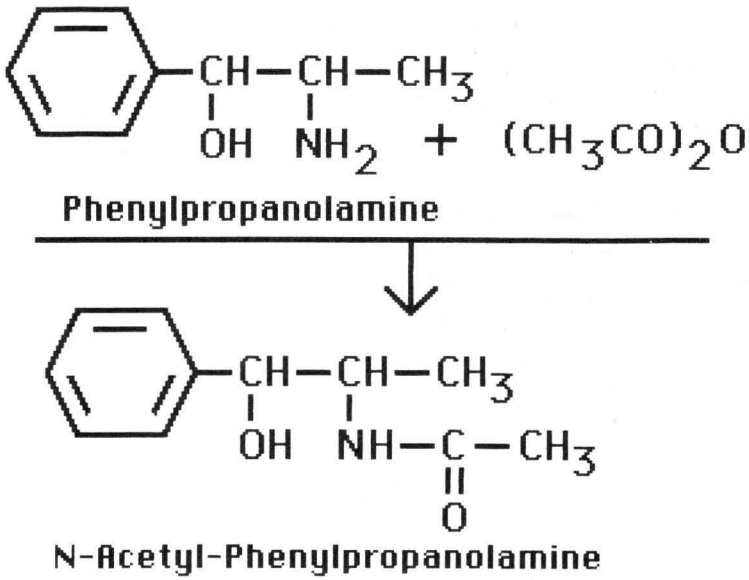
Method A:

100 Grams of N-acetyl-phenylpropanolamine is mixed with 200 mL of normal hydrochloric acid and refluxed for one hour. The solvent is distilled to leave a residue of norpseudoephedrine hydrochloride. Yields are 70 % theoretical.

Method B:

100 Grams of N-acetyl-phenylpropanolamine is mixed with concentrated hydrochloric acid and heated with a small flame until the solution becomes transparent. The solution is then distilled to leave a residue of wet norpseudoephedrine hydrochloride. The hydrochloride salt is then dried in a desiccator over anhydrous Epsom salt. Yields are theoretical.
Reference: (Kanao 1928)

Preparation of N-Acetyl-Phenylpropanolamine From Phenylpropanolamine (Norephedrine)

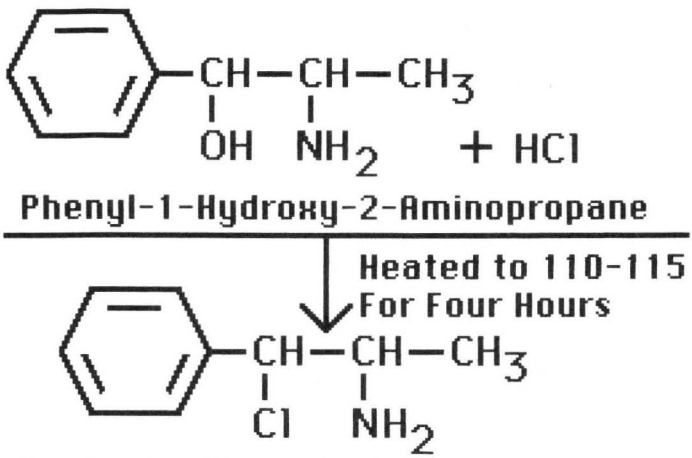


100 Grams of phenylpropanolamine hydrochloride is dissolved in a minimum quantity of water. 300 Grams of potassium carbonate and 500 mL of ether or appropriate solvent are added. 95 mL of acetic anhydride is slowly added to the solution with rapid stirring until the solution becomes neutral. The ether layer is decanted and dried by mixing with anhydrous Epsom salt or potassium carbonate. The solution is filtered of the drying material and distilled to leave a residue of N-acetyl-phenyl-propanolamine. M.P. 135 degrees. Yields are 90 % theoretical.

Reference: (Kanao 1928)

Methamphetamine From Ephedrine

Preparation of Phenyl-1-Chloro-2-Aminopropane From Phenylpropanolamine



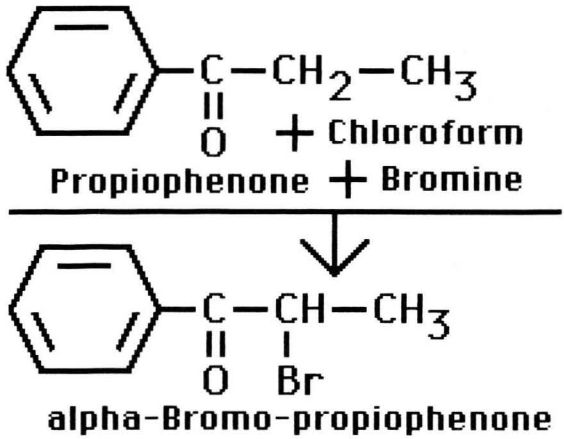
50 Grams of phenylpropanolamine is mixed with 800 mL of concentrated hydrochloric acid in a bomb tube. The tube is heated at 110-115 degrees for four hours. The solution is then cooled to precipitate the phenyl-1-chloro-2-aminopropane which is then collected by suction filtration. Yields are approximately 50 % theoretical.

The chloro derivatives can be transformed into amphetamine by reduction.

References: (Allen 1987) (Cantrell 1988)

CHAPTER 15

PREPARATION OF AMINOKETONE; CATHINONE

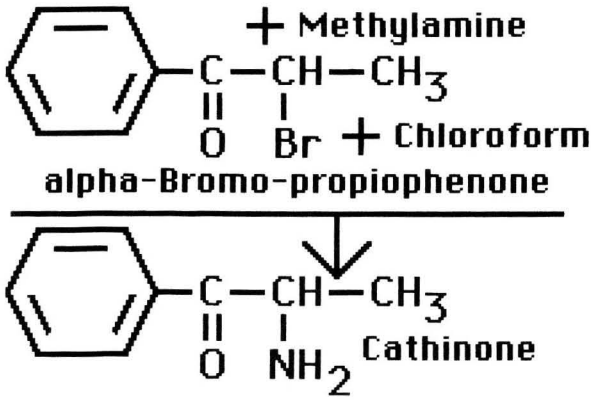


Preparation of alpha-Bromopropiophenone

Solution A: One mole of substituted propiophenone is dissolved in 500 mL of chloroform.

Solution B: One mole of bromine is mixed with 250 mL of chloroform.

Solution A is cooled to 20 degrees and solution B is gradually added, with stirring, over the course of 90 minutes with continued cooling. The mixture is continued to be stirred for 120 minutes at room temperature. Air is then bubbled through the solution for a period of one-half hour. The solution is washed with baking soda, washed with water and then dried with appropriate drying agent. The solution can be evaporated to leave the alpha-bromopropiophenone or the solution (store in refrigerator) can be used in the next reaction to form the aminoketone.



Preparation of alpha-Methylaminopropiophenone

Solution A: The previous crystals of alpha-bromo-propiophenone are dissolved in 150 mL of chloroform (or use previous solution).
Solution B: 0.5 Mole of methylamine is dissolved in 75 mL of water.

Solution A is brought to a temperature of 35 to 40 degrees and rapidly stirred. Solution B is slowly added, dropwise, as the solution is continued to be stirred rapidly. This addition takes approximately one-half hour. The solution is continued to be stirred for 90 minutes at 35 to 40 degrees.

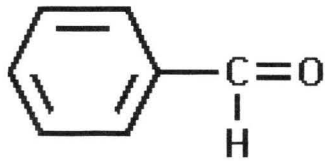
The chloroform layer is repeatedly washed with water, dried and the solvent is evaporated. The gummy residue is dissolved in ether, cooled and a cooled solution of hydrochloric acid is added to precipitate the cathinone hydrochloride which is collected by suction filtration.

Starting Molecule: 2,5-Dimethoxy-alpha-bromopropiophenone
Product: 2,5-Dimethoxy-alpha-methylpropiophenone
Reference: (Morishita 1961)

Starting Molecule: Propiophenone
Product: alpha-Methylpropiophenone (cathinone)
Reference: (Heinzelman 1953)

Cathinone is also prepared by the oxidation of phenylpropanolamine (Parke 1957).

CHAPTER 16: SUBSTITUTED BENZALDEHYDES

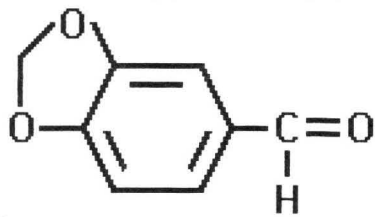


BENZALDEHYDE

Benzaldehydes are used in fragrances, flavorings and in industry. Naturally occurring benzaldehydes can be extracted (e.g. benzaldehyde from oil of bitter almonds, syringic aldehyde from Lilac bark). Most substituted benzaldehydes are produced synthetically because they only occur as trace constituents in natural products. Benzaldehydes are primarily produced by synthetic or semi-synthetic methods.

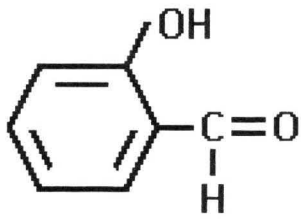
Synthetic substituted benzaldehydes can be made by the following reactions:

1) The partial **oxidation** of substituted propenylbenzenes (e.g. isosafrole which is 3,4-methylenedioxy-propenylbenzene) transforms them into benzaldehydes (e.g. Piperonal, which is 3,4-methylenedioxybenzaldehyde) (Davies 1943) (McLang 1925, 1926). Piperonal can also be prepared by the oxidation of piperic acid (obtained from pepper corns) (Ber 23: 2372).



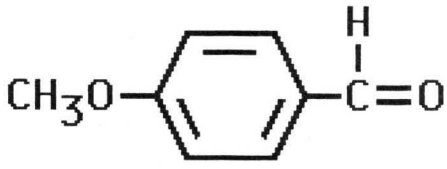
Piperonal

2) The **Reimer-Tiemann Reaction** creates benzaldehydes from phenols (hydroxy benzenes), chloroform and alkali, such as salicylic aldehyde from phenol; 2-Hydroxy-5-methoxy-benzaldehyde from quinol monomethyl ether (Rubenstein 1925).

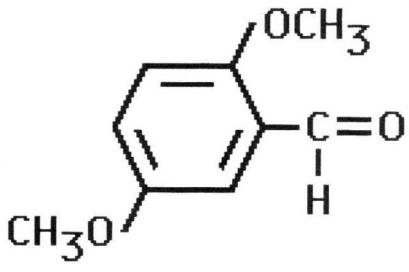


Salicylic Aldehyde

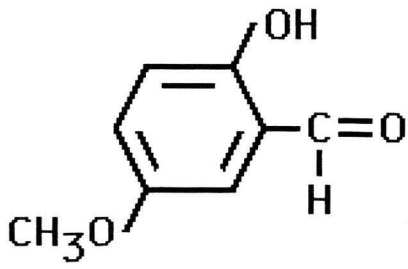
3) The Gattermann Aldehyde Synthesis; from benzenes, cyanide, hydrogen chloride and a Lewis Acid (e.g. p-anisaldehyde, which is 4-methoxybenzaldehyde can be made from anisole (methoxybenzene); 2,5-dimethoxy-benzaldehyde from para-dimethoxybenzene) (Baker 1938) (Niedzielski 1941) (Orinak 1966).



Anisaldehyde



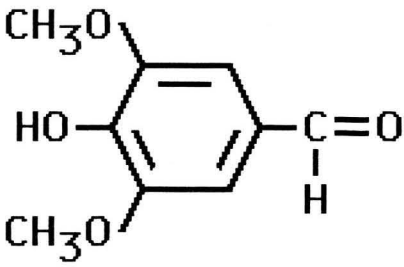
2,5-Dimethoxybenzaldehyde



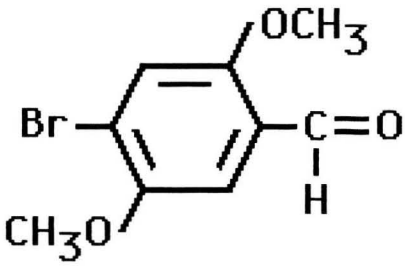
2-Hydroxy-5-methoxy-benzaldehyde

4) The Duff Reaction is used to make ortho-substituted benzaldehydes from substituted phenols with hexamethylenetetramine and an acid catalyst:
e.g. 2-hydroxy-benzaldehyde from phenol (hydroxybenzene);
2-hydroxy-5-methoxybenzaldehyde from p-methoxyphenol.

5) Electrolytic reductions can be used to produce substituted benzaldehydes from benzoic acids (e.g. salicylic aldehyde from salicylic acid). (Balakrishnan 1970) (Dey 1953) (May 1950) (Tesh 1924) (Udupa 1961)



Syringaldehyde

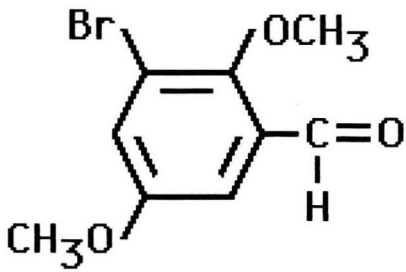


4-Br-2,5-Dimethoxybenzaldehyde

6) Halogenation Reactions are used to create substitutions on benzaldehydes.

4-Br-2,5-Dimethoxybenzaldehyde is created by the bromination of 2,5-dimethoxybenzaldehyde (Nichols 1970).

3-Br-2,5-Dimethoxybenzaldehyde is created by the bromination of 2,5-dimethoxybenzaldehyde (Rubenstein 1925).



3-Br-2,5-Dimethoxybenzaldehyde

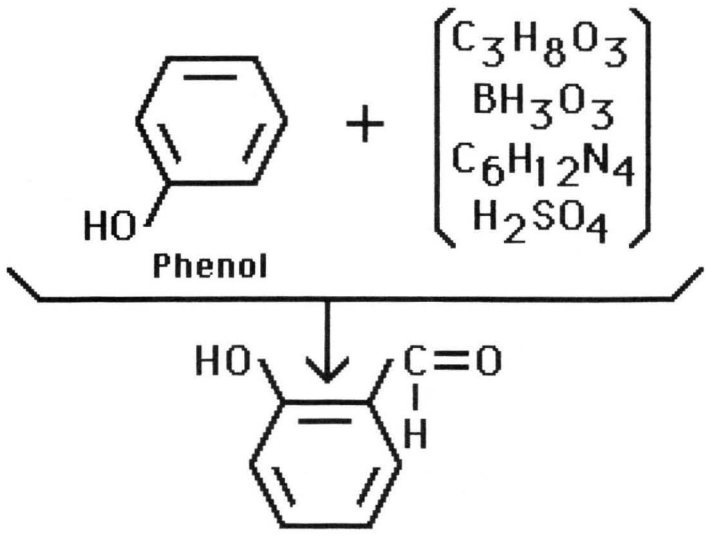
2-Bromo-4,5-dimethoxybenzaldehyde is created by the bromination of 4,5-dimethoxybenzaldehyde (Parijs 1930).

2-Bromo-4,5-methylenedioxybenzaldehyde is created from the bromination of 4,5-methylenedioxybenzaldehyde (Parijs 1930).

5-Bromo-2,4-dimethoxybenzaldehyde is created from the bromination of 2,4-dimethoxybenzaldehyde (Rao 1929).

DUFF REACTION
ortho Formylation of Phenol

An aldehyde group (formyl group) can be attached ortho to the hydroxy group on the benzene ring.



Phenol

ortho-Hydroxybenzaldehyde

The previous reaction involves the ortho-formylation of phenol. When the ortho position is occupied by such groups as methoxy or a carboxylic acid then the formylation takes place on another position on the benzene ring.

A solution of 550 mL glycerine and 160 g. of boric acid is stirred and heated to exactly 170 degrees. The boiling flask is equipped with a downward condenser to distill the water as formed. 120 Grams of hexamine is added and the temperature is allowed to drop to 160 degrees. 0.75 Mole of the phenol is added. The temperature of the solution is raised to 140. The temperature is slowly increased until the reaction becomes exothermic (gives off heat-energy). The temperature of the reaction is kept between 155-160 degrees for 7 minutes while stirring. The temperature is rapidly cooled to 110 degrees.

A solution of 140 mL of concentrated sulfuric acid and 460 mL of water is added to the mixture and stirred for one hour. The mixture is cooled in an ice bath to precipitate the boric acid. The boric acid is suction filtered from the cold solution.

Some of the benzaldehydes can be obtained by steam distillation. Some do not steam distill. Those that are not easily steam distilled can be obtained by extracting with chloroform or appropriate solvent.

The benzaldehyde is extracted from the solvent by mixing with 150 grams of sodium bisulfite. The sodium bisulfite solution is separated and acidified with sulfuric acid.

Sulfur dioxide gas is generated and must be vented.

The aqueous sodium bisulfite solution is heated on a steam bath. When the solution becomes warm, air is then bubbled through the solution until the smell of rotten eggs is not apparent (sulfur dioxide). The solution is cooled to precipitate (as an oil or as crystals) the hydroxy-aldehyde.

Starting Molecule: m-Cresol
Product: 2-Hydroxy-4-methylbenzaldehyde (Ono 1973)
Product: 3-Hydroxy-p-tolualdehyde (Duff 1941)

Starting Molecule: o-Cresol
Product: 2-Hydroxy-m-tolualdehyde Reference: (Duff 1941)

Starting Molecule: p-Cresol
Product: 4-Hydroxy-m-tolualdehyde Reference: (Duff 1941)

Starting Molecule: o-Ethylphenol
Product: 3-Ethyl-salicylaldehyde
Reference: (Renz 1947)

Starting Molecule: p-Methoxyphenol
Product: 2-Hydroxy-5-methoxybenzaldehyde
Reference: (Yakovlev 1950)

Starting Molecule: Phenol
Product: 2-Hydroxy-benzaldehyde
Reference: (Duff 1941)

Starting Molecule: Pyrogallol-1,3-dimethyl ether
Product: 4-Hydroxy-3,5-dimethoxybenzaldehyde
Common Name: Syringaldehyde
Reference: (Allen 1963)

Elbs Persulfate Oxidation of Benzaldehydes

The oxidation of phenols with potassium persulfate to form p-dihydroxy molecules is called the Elbs Persulfate Oxidation Reaction. When the para position is occupied, ortho substitution will occur.

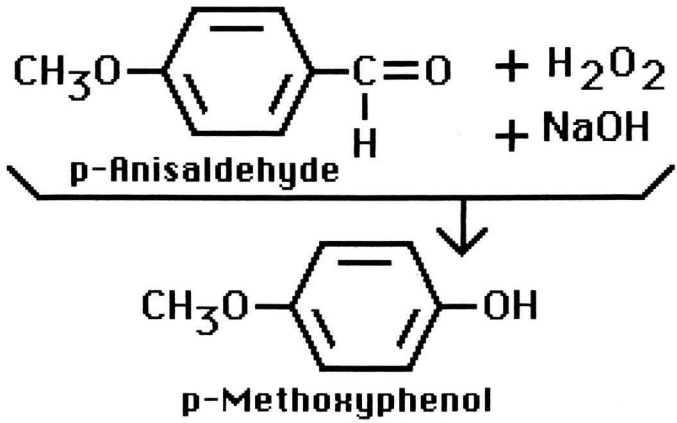
Starting Molecule: Coumarin
Product: 6-Hydroxy-coumarin Reference: (Bargellini 1915)

Starting Molecule: Phenol
Product: Quinol Reference: (Baker 1948)

Starting Molecule (Common Name): Salicylaldehyde
(Chemical Name): 2-Hydroxybenzaldehyde
Product: 2,5-Dihydroxybenzaldhyde
Reference: (Baker 1948) (Hodgson 1927)

Starting Molecule: Vanillin
Product: 3,4-Dihydroxy-5-methoxybenzaldehyde
Reference: (Baker 1948)

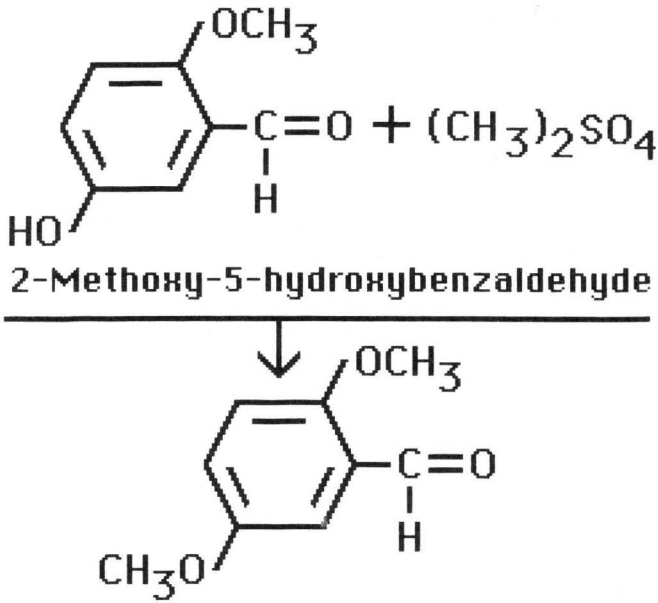
DAKIN REACTION
Preparation of Phenols From Benzaldehydes



0.8 Moles of substituted benzaldehyde is mixed with 350 mL of a sodium hydroxide solution (32 grams of sodium hydroxide). The mixture is stirred to dissolve as nitrogen gas is bubbled into the flask. 1150 mL of 3 % hydrogen peroxide solution is added in 50 mL amounts making sure that the temperature of the solution remains between 40-50 degrees. The solution is allowed to cool to 45 degrees after each addition before another 50 mL is added. The entire addition of hydrogen peroxide will take approximately 1 to 2 hours. When all the hydrogen peroxide has been added, the solution is allowed to cool to room temperature and saturated with sodium chloride (salt). The solution is extracted with 800 mL of ether or appropriate water insoluble solvent. The extract is dried and the solvent distilled to leave a residue of the substituted phenol. Yields are approximately 75 % theoretical.

Starting Molecule: 2-Hydroxy-3-methoxybenzaldehyde
Product: Pyrogallol monomethyl ether
Reference: (Surry, Organic Syntheses)

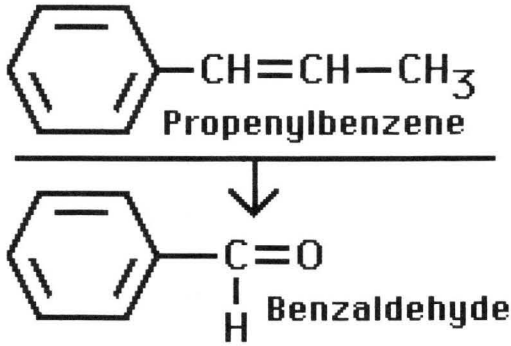
METHYLATIONS OF HYDROXYBENZALDEHYDES



0.25 Mole of hydroxybenzaldehyde is melted in a boiling flask equipped with a condenser for reflux. 33 mL of 50 % potassium hydroxide solution is added dropwise, with stirring at a rate of 2 to 3 drops per second. 32 mL of dimethyl sulfate is then added at a rate of of 2 to 3 drops per second with stirring. Two hours later the reaction mixture is poured into a beaker, and rapidly cooled (approx. 25 degrees) by pouring onto ice-cold water. The precipitated crystalline mass is suction filtered from the solution (oils are extracted with ether and distilled to leave the methoxybenzaldehyde), ground to powder and mixed with 80 mL of ice-water, suction filtered again and dried over anhydrous magnesium sulfate in a vacuum desiccator or covered casserole dish. Benzaldehydes are highly sensitive to oxidization by air and should be stored in a tightly sealed amber bottle. Yields are 80 %+.

References: (Buck; Organic Syntheses) (Arthur 1959)

PREPARATION OF SUBSTITUTED BENZALDEHYDES FROM SUBSTITUTED PROPENYLBENZENES



Method A can be used with hydroxy, methoxy and methylenedioxy substitutions.

Method A: 1 Mole of substituted propenylbenzene is added to a cupric oxide solution (1900 grams of cupric sulfate pentahydrate, 1070 grams of sodium hydroxide, and 2500 mL of water). The mixture is refluxed for eight hours and filtered of red cuprous oxide. The filtrate is washed with water. The alkaline filtrate and washings are acidified and extracted with ether (or appropriate solvent e.g. benzene, acetone etc.). The acidified solution is mixed for one hour with a solution of 200 grams of sodium bisulfite in 750 mL water. The aqueous layer is separated, washed with appropriate solvent and acidified with a 50 % solution of sulfuric acid. The solution is heated on a steam bath for short period and air is bubbled through the solution to remove sulfur dioxide. The substituted benzaldehyde crystallizes from the solution on cooling and is separated by vacuum filtration. Yields are approximately 90 %.

Various alkaline copper oxidizing agents (e.g. Fehling's Solution, Benedict's Solution) will produce the same results.

Alkaline copper oxidizing agents are best suited for the oxidization of propenyl group to an aldehyde group. The oxidizing strength of changing a cupric to a cuprous compound is adequate to transform the propenyl to the aldehyde group, but not strong enough to oxidize the benzaldehyde into benzoic acid.

Method B: 1 Mole of substituted propenylbenzene is thoroughly mixed with a solution of 800 grams of 50 % sulfuric acid in five liters of water. 200 grams of sodium dichromate in one liter of water is gradually added at 30 to 40 degrees over the period of 30 minutes. The mixture may turn green. Extract the mixture with 3 liters of benzene. Wash the benzene extract with one liter of 5 % sodium hydroxide solution and then wash with 3 liters of water. The solvent is distilled from the solution to leave a crude residue of oily 'wet' substituted benzaldehyde which is dried over anhydrous calcium chloride, Epsom salt or appropriate drying agent. The crude product can be purified by dissolving in minimum quantity of hot alcohol, filtered through animal charcoal and concentrated to crystallize the substituted benzaldehyde.

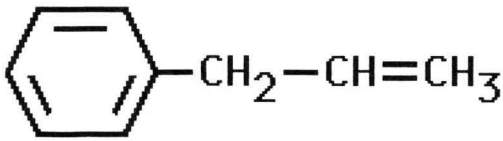
Starting Molecule: 4-Hydroxy-3,5-dimethoxypropenylbenzene
Product: 4-Hydroxy-3,5-dimethoxybenzaldehyde
Common Name: Syringaldehyde
Reference: (Pearl 1950)

Starting Molecule: 3,4-Methylenedioxypropenylbenzene
Product: 3,4-Methylenedioxybenzaldehyde
Common Name: Piperonal
Reference: (Davies 1943)

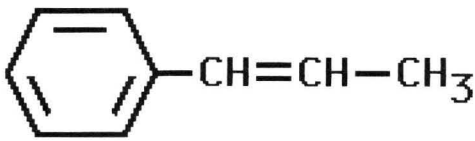
See also (McLang 1925, 1926)

CHAPTER 17: SUBSTITUTED PHENYLPROPENES (ALLY AND PROPENYLBENZENES) FROM NATURAL SOURCES

Substituted phenylpropenes can be obtained by crystallization from commonly available natural essential oils. Essential oils can be obtained by the steam distillation or solvent extraction of many plants, roots, bark and seeds.



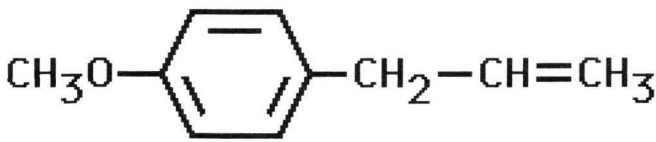
3-Phenylpropene also called Allybenzene



1-Phenylpropene also called Propenylbenzene

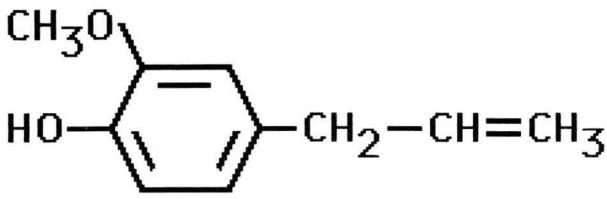
The best way to obtain the essential oils from botanicals is by steam distillation. The distillate forms two layers. One layer is water and the other layer is the water insoluble essential oil. Another way is to grind the botanical into small granular chunks and do a percolation (or mix the material with the solvent and filter) with a water insoluble solvent such as ether, benzene, toluene, acetone, chloroform etc. The solvent is distilled or evaporated to leave the essential oil.

Essential oils must be kept in a tightly sealed amber bottle and stored in a cool place as phenylpropenes will oxidize with air and polymerize with light.



Estragol

Estragol (4-methoxy-allybenzene) can be obtained from crude sulfate turpentine or Tarragon Oil (*Artemisia dracunculus*). Estragol forms azeotropic (partially dissolves) mixtures with water. (Booth 1968).



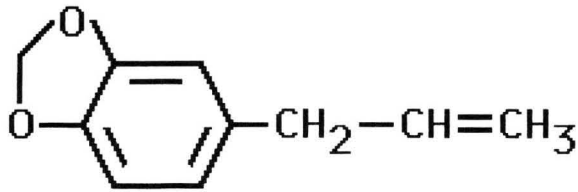
Eugenol

The Oil of Clove contains approximately 75 % eugenol, which is 3-methoxy-4-hydroxyallybenzene. It can be extracted by the steam distillation of cloves and crystallization when cooled. The melting point of eugenol is -9.2 degrees C.

Sassafras Oil

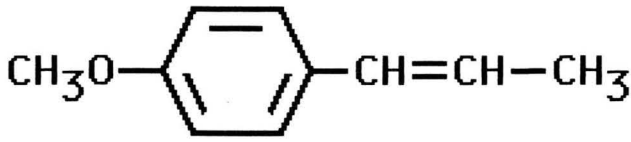
Sassafras Bark Oil is obtained by the steam distillation of the inner bark chips of the Sassafras tree (*Sassafras albidum*, *S. variifolium* and *S. albidum*).

The distillation of Sassafras bark was an American Industry at one time. It used to be an economic base for Ohio, New Jersey, Indiana, Tennessee, New York and New England during and after the civil war. During the 1940's, Virginia, Maryland and Pennsylvania were the major producers. Today much of the natural Sassafras Oil comes from the exploitation of a tree in the Brazilian rain forest named Ocotea pretiosa.



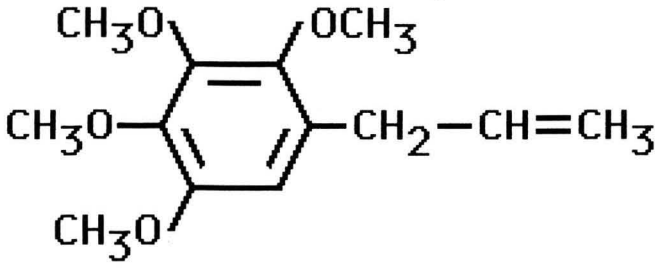
Safrole; (3,4-methylenedioxyallybenzene)

The oil is extracted from the inner bark of the Sassafras tree by steam distillation. The root bark contains between 6 to 9 percent oil. Sassafras oil contains approximately 80 % safrole. Safrole can be suction filtered from the oil by crystallizing the oil at dry ice temperature. Safrole solidifies at about 11 degrees. Synthetic Prep.: (Feugeas 1964; Perkin 1927).



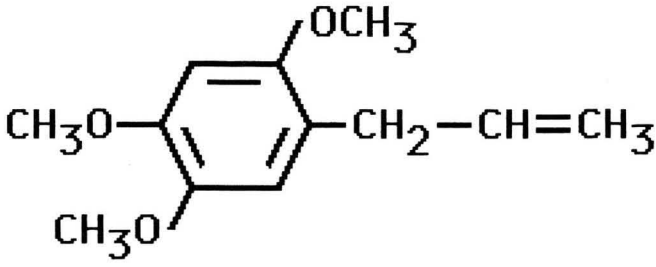
Anethole

The chief constituent of anise seed oil is anethole (4-methoxy-propenylbenzene) which occurs in the oil from 80-90 %. Anethole maybe obtained from the seed oil by placing the oil in a beaker, cooling it in the freezer to crystallize the anethole and suction filtration. The Oil of Fennel Seed (*Foeniculum vulgare*) contains approximately 50 to 60 % anethole. The m.p. of anethole is 21 degrees.



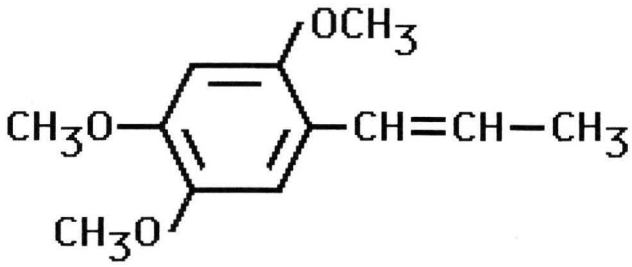
2,3,4,5-Trimethoxyallybenzene

2,3,4,5-Trimethoxyallybenzene is a constituent of the seed oil of *Apium* species.



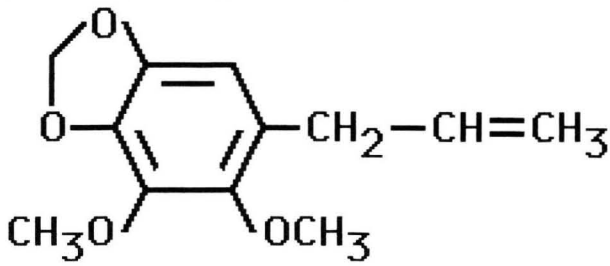
2,4,5-Trimethoxyallybenzene

The oil of *Caesulia axillares* contains 2,4,5-trimethoxyallybenzene.



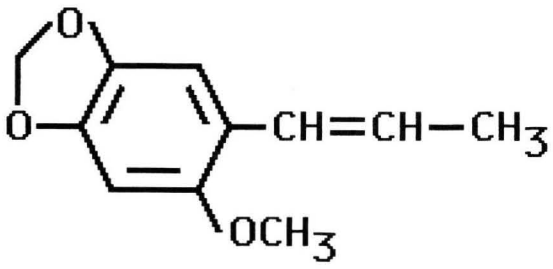
Asarone

Sweet Flag Oil is obtained by the steam distillation of the roots of *Acorus calamus* (sweet flag), *Asarum europaeum* and *Asarum arifolium*. The oil contains about 75 % asarone (2,4,5-trimethoxypropenylbenzene). Asarone can be suction filtered from the crystallized oil that has been exposed to low temperature. Asarone occurs as two isomers in nature. Alpha asarone is also called the trans isomer. ß-Asarone is called beta-asarone and is the cis isomer. The m.p. of asarone is 67 degrees. Synthetic preparation of 2,4,6-Trimethoxypropenyl-benzene: (Holms 1950). ß-Asarone can also be prepared synthetically (Shulgin 1965) from the decarboxylation of alpha-Methyl-ß-2,4,5-trimethoxy-phenylacrylic acid with copper gauze and quinoline (Dandiya 1962).



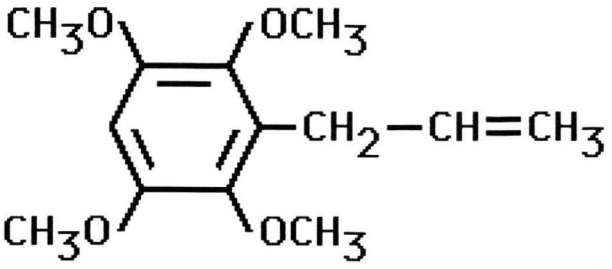
Dill Apiol

The Oil of Dill Seed is obtained by the steam distillation of dill seeds (*Anethum graveolus*). Dill apiol, (2,3-dimethoxy-4,5-methylenedioxyallybenzene, can be isolated from this oil. Dill apiol has a m.p. of 29.5 degrees.
Synthetic Preparation: (Baker 1934) (Dalacker 1969).



Carpacin

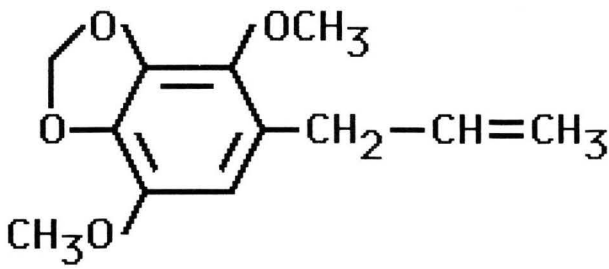
2-Methoxy-4,5-methylenedioxypropenylbenzene, carpacin, is a constituent of *Cinnamomum* species from Bougainville.



2,3,5,6-Tetramethoxyallybenzene

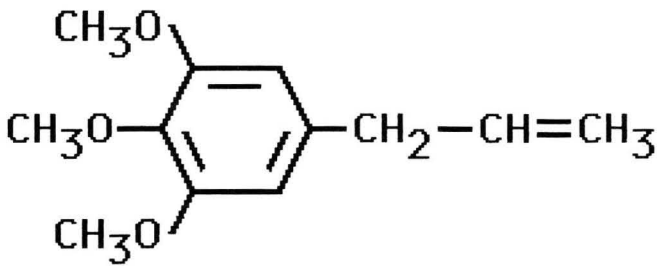
2,3,5,6-Tetramethoxyallybenzene and Apiol (3,4-methylenedioxy-2,5-dimethoxy-allybenzene) from Parsley Seeds.

Chopped parsley seeds are soaked in ethyl alcohol for two days. The alcohol is filtered from the seeds. The solution is cooled to 10-12 degrees and the crystallized 2,3,5,6-tetramethoxyallybenzene is suction filtered from the solution. Evaporation of the ethanol leaves apiol containing various flavonoglycosides. The solution is washed with water and the non-aqueous layer is refrigerated to crystallize the apiol. Apiol occurs as brittle, white, needle shaped crystals, m.p. 30 degrees. (Kolesnikov 1958)



Apiol (Parsley)

Apiol is the chief constituent of parsley seed oil. Apiol was first obtained from the oil by Stange of Basel, Switzerland in 1823. In 1890 Ciamician and Silber identified the chemical structure of apiol to be 3,4-methylenedioxy-2,5-dimethoxy-allybenzene. Synthetic Preparation: (Baker 1938)



Elemicin

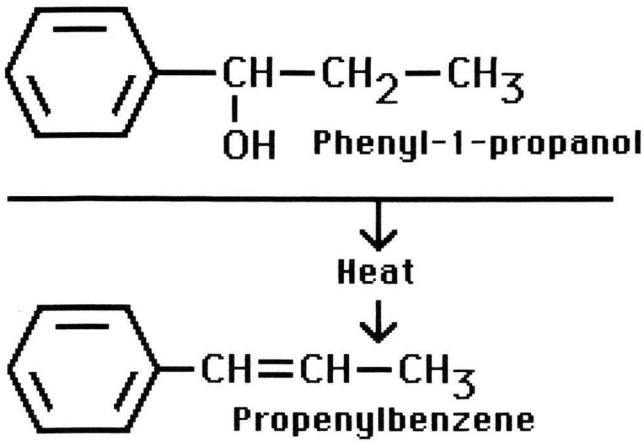
Elemicin, also called 3,4,5-trimethoxyallybenzene, can be obtained from nutmeg oil (Shulgin 1967) or produced synthetically from eugenol (Dandiya 1962) (Rao 1949).

Synthetic Preparation of Myristicin (1-Methoxy-2,3-methylenedioxy-5-allybenzene): (Rao 1949) (Trikojus 1949).

Safrole is listed as a carcinogen by the EPA. See: Second Annual Report on Carcinogens (NTP 81-43, Dec. 1981; pgs. 219-220); IARC Monographs (1976) 10: 231-241

PROPENYLBENZENES FROM PHENYLPROPANOLS

Phenylalkenes such as propenylbenzene can be created by the dehydration of phenyl-1-propanols. This reaction is carried out by heating 1-phenyl-1-propanol with alumina (aluminum oxide) or vermiculite. 3-Phenyl-1-propanol will produce allybenzenes.



Propenylbenzene from Phenyl-1-propanol

A) By Boiling with Alumina:

1-Phenyl-1-propanol (0.25 moles) is mixed in a distillation apparatus with 75 g. alumina and a pinch of hydroquinone (p-dihydroxybenzene) or pyrogallol (inhibitor). The mixture is heated under a vacuum for 1 hour at 150 degrees. The mixture is washed, in a separatory funnel with a dilute solution of sodium hydroxide and then water. The water insoluble layer is dried over anhydrous calcium chloride, sodium sulfate or magnesium sulfate. 85 % yields of propenylbenzene are obtained.

Starting Molecule: 1-(4-Methoxyphenyl)-1-propanol
Product: Anethole; (4-Methoxypropenylbenzene)
Reference: (Müller 1957)

B) By Heating With Vermiculite:

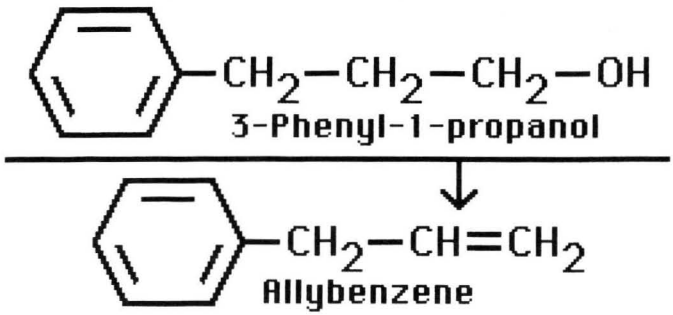
0.25 Mole of 1-phenyl-1-propanol is heated at 90 degrees for five minutes (under reduced pressure) with 3 mL of concentrated sulfuric acid on 8 grams of vermiculite. The mixture is cooled and washed with a dilute solution of sodium hydroxide and water. The water insoluble layer is dried.

Starting Mol.: 1,1-Dimethyl-2-hydroxy-2-(p-methoxyphenyl)ethane
Product: 1,1-Dimethyl-2-(p-methoxyphenyl)ethene
Reference: (Bruce 1952)

C) By Heating With Potassium Bisulfate:

Starting Molecule: 1-(1,3-Benzodioxol-5-yl)butan-1-ol
Product: 1-(1,3-Benzodioxol-5-yl)butene
Reference: (Nichols 1985)

Allybenzene From 3-Phenyl-1-propanol By Thermal Dehydration



Pyrolysis Apparatus

A quartz or high temperature Pyrex tube (e.g. combustion tubing), approximately 2 mm thickness, 20 mm in diameter, one foot long is used in this apparatus. Ten inches of the tube is filled with activated alumina (8 to 14 mesh) which is held in place with wire gauze and a metal spring. An iron-constant thermocouple lead is placed in a glass tube which is positioned half way up on the outside of the tube. The

entire tube is heated by a Nichrome wire or heating tape wrapped around it and regulated by a variable transformer.

The receiving flask is connected to a vacuum outlet and is immersed in a Dry Ice-alcohol bath. One mole of the propanol containing a pinch of pyrogallol (inhibitor) is placed in a dropping funnel at the top of the column and slowly dripped into the column at a rate of one drop per second. The temperature is maintained at 300 degrees under a vacuum of 20-25 mm. (water aspirator).

The reaction may be carried out at atmospheric pressure, but the top of the column must be closed to force the vapors down the column. A yellow liquid separates from the water formed during the dehydration. The yellow liquid is washed with dilute sodium hydroxide and water or aqueous sodium carbonate to remove any adhering inhibitor. The product is then dried over anhydrous calcium chloride or magnesium sulfate. Yields 80 to 85 %.

Starting Molecule: p-Ally-ß-phenethyl alcohol
Product: p-1-Propenylstyrene (p-Propenylvinylbenzene)
Reference: (Overburger 1951, 1954)

Starting Molecule: Hydrocinnamyl acetate
Product: Allybenzene Reference: (Fort 1955)

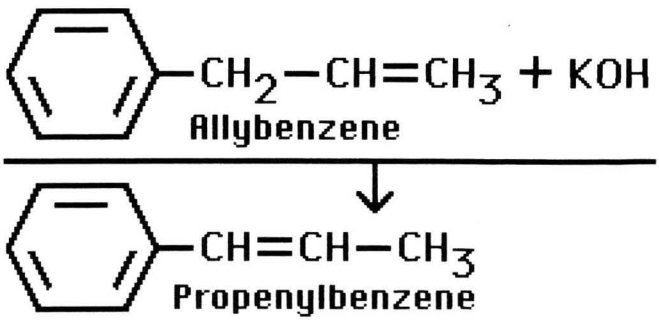
Starting Molecule: p-Methoxy-hydrocinnamyl acetate
Product (Chemical Name): p-Methoxy-allybenzene
Product (Common Name): Estragole Reference: (Fort 1955)

Propenylbenzenes From Allybenzenes

One mole of allybenzene is mixed with a small amount pyrogallol (inhibitor) and passed dropwise through the column. The temperature is maintained at 300 degrees at 20-25 mm. The resulting light yellow liquid is washed with a dilute sodium hydroxide solution then water and dried over anhydrous calcium chloride. Yields are over 80 %.

Starting Molecule: Allybenzene
Product: 1-Propenylbenzene
Reference: (Frisch 1959)

PROPENYLBENZENES FROM ALLYBENZENES



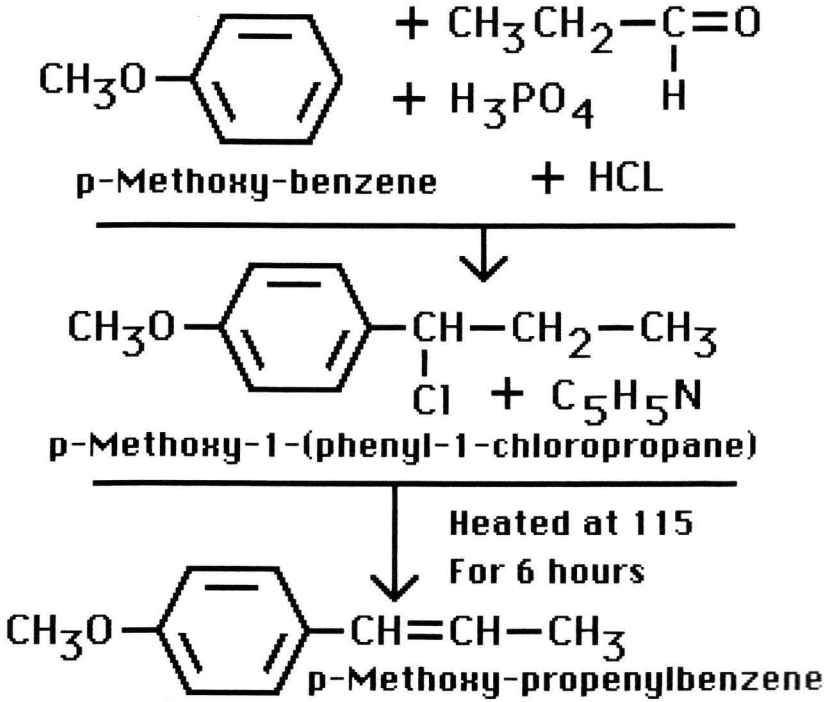
Starting Molecule: 3-Methoxy-4,5-methylenedioxyallybenzene
Product: 3-Methoxy-4,5-methylenedioxypropenylbenzene
Reference: (Trikojus 1949)

Starting Molecule: 2,3,4-Trimethoxyallybenzene
Product: 2,3,4-Trimethoxypropenylbenzene
Reference: (Shulgin 1965)

Starting Molecule: 2,3,5-Trimethoxyallybenzene
Product: 2,3,5-Trimethoxypropenylbenzene
Reference: (Shulgin 1965)

Starting Molecule: 2,4,6-Trimethoxyallybenzene
Product: 2,4,6-Trimethoxypropenylbenzene
Reference: (Holmes 1950) (Shulgin 1965)

Quelet Reaction
Preparation of Para-substituted Propenylbenzenes From Para-substituted Benzenes



3 Moles of p-methoxybenzene is mixed with 3 moles of propionaldehyde, 250 mL of concentrated hydrochloric acid and 75 grams of phosphoric acid. This solution is placed in a tall graduated cylinder. The flask is equipped with a magnetic stirrer and a two hole stopper. One glass tube is run from a hydrogen chloride gas source through the stopper and to the bottom of the glass cylinder (above the stir bar). A gas diffusion stone, made of an inert material such as a glass filter, is attached at the end of the glass tubing. Another glass tube is attached to the other hole on the stopper. This tube is run through several traps containing water to absorb hydrogen chloride gas that exits the apparatus.

The solution is cooled to 5 degrees and saturated with anhydrous hydrogen chloride gas for 2.5 hours with stirring. The solution is then poured on ice and extracted with petroleum ether. The p-methoxy-1-(phenyl-1-chloropropane) should not be distilled as the material will decompose to form phenylpropene, polymerized products and hydrochloric acid). The petroleum ether extract contains the crude p-methoxy-1-(phenyl-1-chloropropane) (approximate 25 to 50 % theoretical yields).

300 grams of pyridine is mixed with the petroleum ether extract of crude p-methoxy-1-(phenyl-1-chloropropane). The petroleum ether is distilled off the solution. The pyridine containing the p-methoxy-1-(phenyl-1-chloropropane) is heated at 115 degrees for 6 hours. The solution is composed of 50% p-methoxypropenylbenzene and 50 % 1,1-bis(p-methoxypropenyl-benzene). The p-methoxy-propenylbenzene is obtained from the solution by:

1) being acidified with dilute hydrochloric acid, and is fractionally distilled.

2) in some propenylbenzenes (such as anethole) can be crystallized from the solution by exposing the solution to a cold temperature (the freezer). Yields are 50 % theoretical.

This reaction is called the Quelet Reaction. It was primarily designed to produce para and methoxy substituted styrenes from methoxy benzene (anisole). Various phenylalkenes can be produced using this reaction. Chain lengths can be shortened or lengthened. If the propionaldehyde is replaced with equal molar amounts of paraldehyde, styrenes will result. If butanal replaces the propionaldehyde, butenylbenzenes will result. Substitutions on the benzene ring should be obtained by replacement of the benzene with equal molar amounts of substituted benzene to produce substituted phenyl-alkenes.

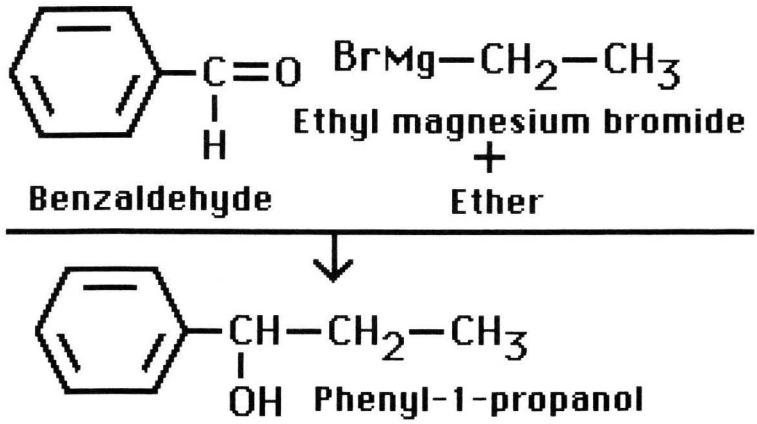
Para-dimethoxybenzene has been reported in one study not to form 2,5-dimethoxypropenylbenzene. As this reaction has not been fully studied, (zinc chloride might be used in place of phosphoric acid, see Blanc Reaction), I speculate that there is much that can be done to increase yields by a more intensive study of chloroalkylation of substituted benzenes. Readers should also review the Blanc (chloromethylation) Reaction. Refs.: (Quelet 1936, 1940, 1943)

Starting Molecule: Anisole (methoxybenzene)
Product: Anethole (4-methoxypropenylbenzene)

Phenyl-1-Propanols Using the Grignard Reagent

The Grignard reaction was originally observed by Barbier in 1899. The reaction was identified as being composed of two stages by Grignard in 1900. The reaction is used to produce a very diversified series of products. In the following, I will only be describing the synthesis of phenyl-1-propanols. I would suggest to any reader that a more explicit description of this reaction will be found in any organic chemistry text.

The reaction includes formation of the Grignard Reagent. It is created by the addition of magnesium to an organo halide forming RMgX. This is done in a solution of ether or appropriate solvent which is non-reactive to the the reagent. Oxygen, water, etc. must be excluded from the reaction as the reaction will occur very rapidly; much too rapidly for the safety of the chemist. Ketones (eg. acetophenone) maybe used in place of the aldehyde (eg. benzaldehyde).



A Grignard reagent is prepared: 0.75 moles of magnesium turnings is mixed with 250 mL of dry ether. One gram of ethyl bromide is added to initiate formation of reagent. More ethyl bromide (in 250 mL dry ether) is added to a total

bromoalkane of 0.75 moles. The mixture is refluxed with stirring until the magnesium has disappeared.

750 mL of dry ether is mixed with 0.5 moles of benzaldehyde and added dropwise with stirring under reflux for a total of four hours. The solution is cooled to 0 degrees and the reaction complex is decomposed with the slow addition of an aqueous solution of ammonium chloride. The aqueous layer is separated and extracted with benzene. The benzene extract is combined with the organic (non-aqueous) layers, dried with Epson salts and evaporated to leave the phenyl-1-propanol.

Starting Molecules: Anisaldehyde & Isopropyl chloride
Product: 1,1-Dimethyl-2-hydroxy-2-(p-methoxyphenyl)ethane
Reference: (Bruce 1952)

Starting Molecule: 3,5-Dimethoxybenzaldehyde
Reagent: n-Hexylmagnesium bromide
Product: 1-(3,5-Dimethoxyphenyl)heptan-1-ol
Reference: (McOmie 1966)

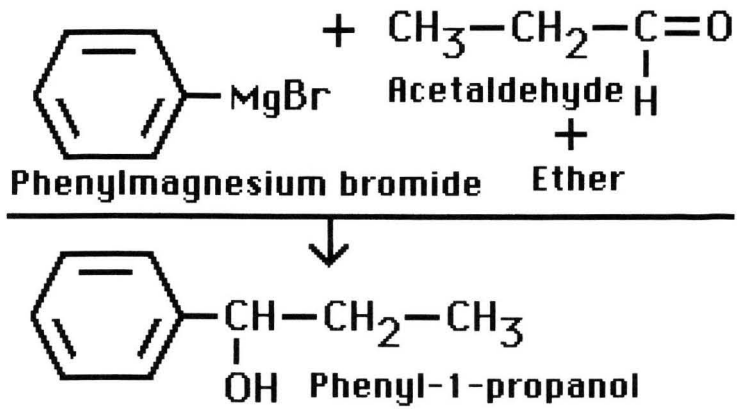
Starting Molecules: 3,5-Dimethoxybenzaldehyde
Reagent: Lauryl magnesium bromide
Product: 3,5-Dimethoxyphenyl(dodecyl)methanol
Reference: (Ridley 1968)

Starting Molecules: 3,5-Dimethoxybenzaldehyde
Reagent: Tetradecyl magnesium bromide
Product: 3,5-Dimethoxy-(1'-hydroxypentadecyl)-benzene
Reference: (Wasserman 1948)

Starting Molecules: 3,4-Methylenedioxybenzaldehyde
Reagent: 1-Bromopropane
Product: 1-(1,3-Benzodioxol-5-yl)butan-1-ol
Reference: (Nichols 1986)

Starting Molecules: Syringaldehyde
Reagent: Ethyl magnesium bromide
Product: 3,5-Dimethoxy-4-hydroxyphenyl-1-propanol
Reference: (Pepper 1964) ; J.A.C.S. 72: 5760 (1950)

Starting Molecule: 3,4,5-Trimethoxybenzaldehyde
Reagent: Alkyl magnesium bromide
Product: 3,4,5-Trimethoxyphenylalkylcarbinols
Reference: (Bailey 1974)

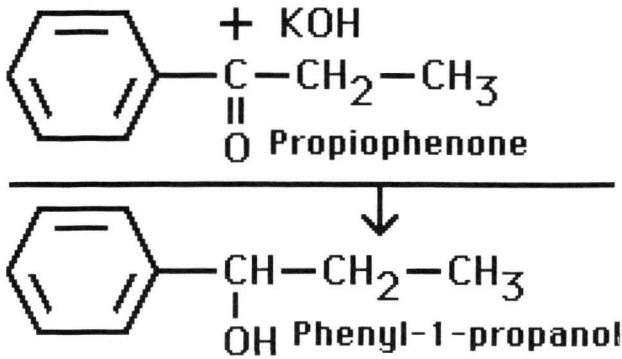


Start. Mol.: 3,4-Methylenedioxybenzene magnesium bromide
Reagent: Acetaldehyde
Product: 3,4-Methylenedioxyphenyl-1-propanol
Reference: (Freugeas 1964)

4-Bromo-1,2-methylenedioxybenzene can be prepared in acetic acid by the bromination of 1,2-methylenedioxybenzene (Jones 1917).

5-Bromo-1,2,4-trimethoxybenzene can be prepared by the bromination of 1,2,4-trimethoxybenzene (Baker 1938).

Phenyl-1-Propanol
By Reduction of Propiophenone



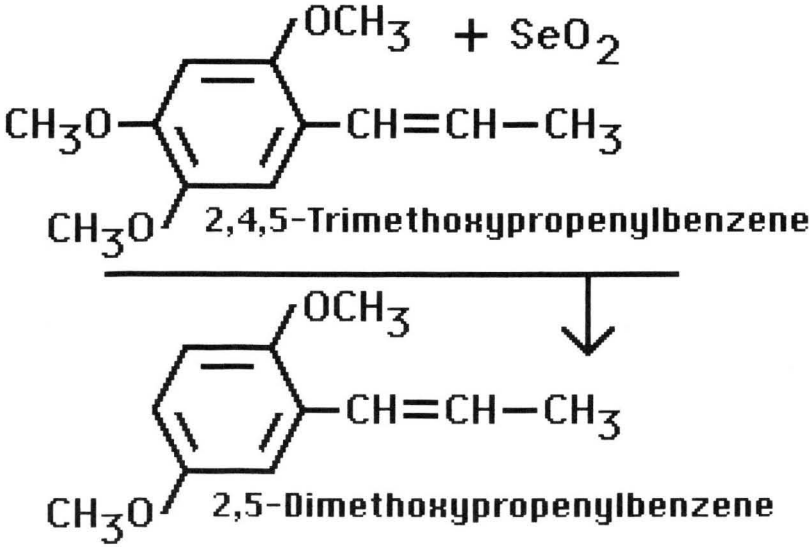
A mixture of 225 mL of ethanol, 70 grams of potassium hydroxide and 0.25 mole of ketone is heated at 200 to 220 degrees in a rocking autoclave for 6 hours. The mixture is mixed with 475 mL of water and the ethanol is distilled. The aqueous solution is extracted with ether; the ether solution is then washed with 10 % potassium hydroxide. The alkaline solution is then acidified and extracted with ether. The ether is distilled and the residue is fractionally distilled to obtain the phenyl-1-propanol.

Methoxy groups crack to form hydroxy groups.

Starting Molecule: Anisyl-3-hexanone-4
Products: 50 % p-Hydroxyphenyl-3-hexanol-4
25 % p-Methoxyphenyl-3-hexanol-4
References: (Rubin 1944)

Preparation of 4-Unsubstituted Propenylbenzenes From 4-Methoxypropenylbenzenes

This reaction cracks off the para methoxy substitute on propenylbenzenes.

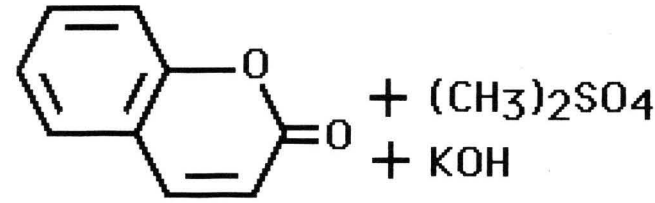


In a boiling flask; 0.5 mole of the para-methoxy substituted propenylbenzene is mixed with 225 mL of ethyl alcohol and 22 grams of selenium dioxide. The solution is refluxed for five hours and then extracted with ether or appropriate solvent. The solvent is distilled under reduced pressure (water aspirator). Two fractions will distill over after distillation of the solvent. One fraction is the para-unsubstituted propenylbenzene and the other is para-unsubstituted phenylpropane.

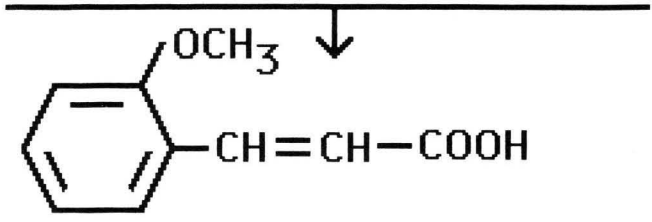
Starting Molecule (Common Name): ß-Asarone
(Chemical Name): 2,4,5-Trimethoxypropenylbenzene
Products: 2,5-Dimethoxypropenylbenzene
2,5-Dimethoxyphenylpropane
Reference: (Rao 1937)

CHAPTER 18: PREPARATION OF CINNAMIC ACIDS

Cinnamic acids can be created from the methylation of coumarins. Methoxy substituted coumarins produce lower yields than do non-substituted and hydroxy substituted coumarins.



Coumarin



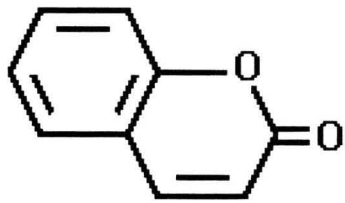
2-Methoxycinnamic acid
(2-Methoxy-phenylacrylic acid)

0.5 Moles of substituted coumarin is mixed with 65 mL of dimethyl sulfate and 70 ml of 33 % potassium hydroxide. The reaction is allowed to complete, cooled and mixed with more dimethyl sulfate and potassium hydroxide. The reaction mixture is refluxed with 150 mL of 33 % potassium hydroxide for one hour. The reaction mixture is then methylated further with more dimethyl sulfate. Potassium hydroxide is added again and refluxed to hydrolyze the methyl ester that is formed. The solution is then mixed with 3 liters of water and filtered through charcoal. The mixture is chilled, mixed with hydrochloric acid to precipitate the cinnamic acid which is collected by vacuum filtration.

Starting Molecule: 6-Hydroxy-4-methylcoumarin
Product: 2,5-Dimethoxy-ß-methylcinnamic acid
Reference: (Woodruff 1942)

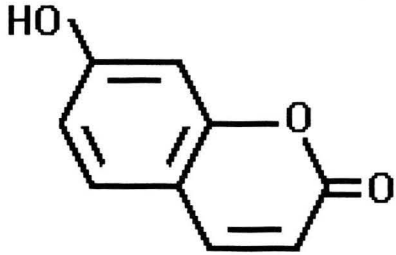
Starting Molecule: 7-Hydroxy-4-methylcoumarin
Product: 2,4-Dimethoxy-ß-methylcinnamic acid
Reference: (Pechman 1884) (Woodruff 1942)

NATURALLY OCCURRING COUMARINS



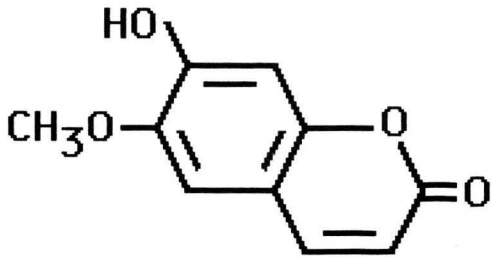
Coumarin

Coumarin occurs in lavender, woodruff *(Asperula)*, tonka beans, and sweet clover *(Melilotus)*. Coumarin can be extracted from sweet clover with hot water. Reference: (Sethna 1945)



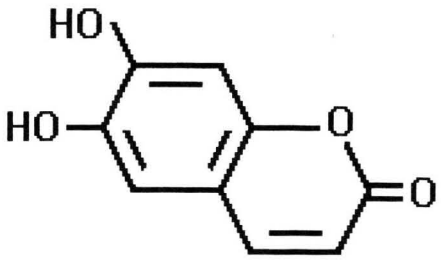
Umbelliferone (7-Hydroxycoumarin)

Umbelliferone can be obtained from the distillation of the resin from *umbelliferae* species of plants.



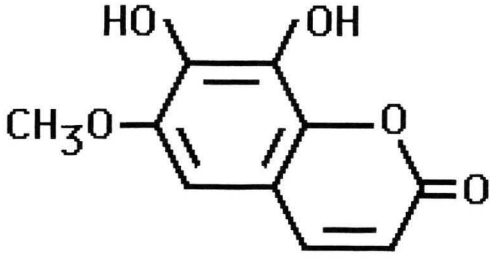
Scopoletin (7-Hydroxy-6-methoxycoumarin)

Scopoletin occurs in *Solanaceae*, *Convolvulacea* and various other species of plants. It can also be made synthetically.



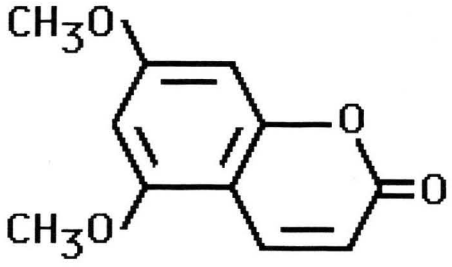
Esculetin (6,7-Dihydroxycoumarin)

Esculetin can be obtained by the hydrolysis of esculin. Esculin occurs in the leaves and bark of the horse chestnut tree *(Hippocastanacea).*



Fraxetin (7,8-Dihydroxy-6-methoxycoumarin)

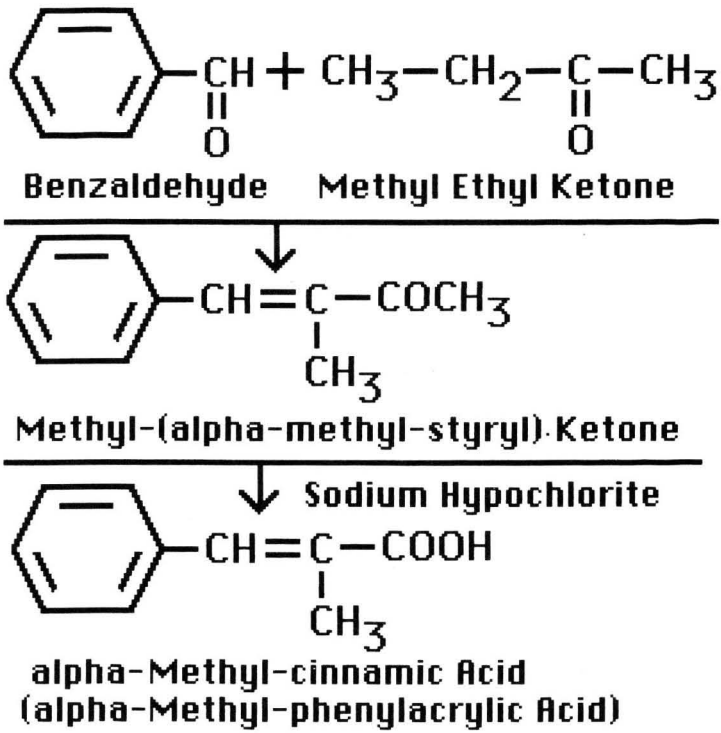
Fraxetin is obtained by heating fraxin with sulfuric acid. Fraxin occurs in the bark of the Common Ash tree *(Fraxinus excelsior).*



Limettin (5,7-Dimethoxycoumarin)

Limettin is obtained from West Indian lime oil and various citrus oils.

CROSSED ALDOL CONDENSATION



Methyl-(alpha-methyl-styryl)-ketone From Benzaldehyde and MEK

Benzaldehyde (0.25 mole) and methyl ethyl ketone (0.5 mole) are mixed together and cooled in an ice salt bath. Hydrochloric acid gas (0.125 mole) is bubbled through the cold mixture. The entire mixture is then placed in a refrigerator (0 to 5 degrees) or in the freezer (-10 to -5 degrees) and shaken for 24 to 48 hours. Ether is then added to the mixture, solid sodium carbonate is used to neutralize the solution. The mixture is then washed with water and dried with anhydrous magnesium sulfate. Yields are approx. 75% to 90 %.

HALOFORM REACTION
alpha-Methyl-Cinnamic Acids
From Methyl-(alpha-methyl-styryl)-ketone

Solution A: The crude methyl-(alpha-methyl-styryl)-ketone (0.25 mole) is dissolved in 500 mL of ethanol.

Solution B: A sodium hypochlorite solution is prepared: Sodium hydroxide (2.5 mole) in 2500 ml of water (cold) to which chlorine (0.75 mole) gas has been bubbled through (keeping cold).

At a temperature of 20 degrees: Solution B is added to Solution A. It takes approximately a quarter of an hour in order to complete the addition and to keep the temperature below 20 degrees.

The mixture is allowed to raise to room temperature and then stirred for approximately one hour. Two layers form, including some solids.

The solution is distilled. Chloroform comes over first, followed by ethanol, then the water and an oily substance. Approximately 620 to 630 mL are collected.

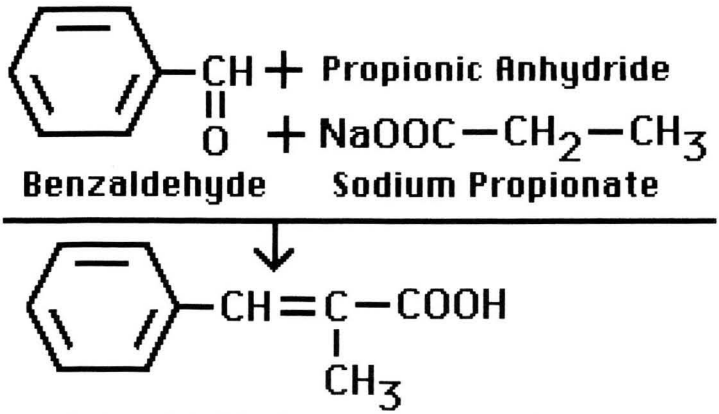
The residue is composed of an aqueous layer and a gummy layer of sodium alpha-methyl-cinnamate. The mixture is cooled; the sodium alpha-methyl-cinnamate solidifies and is removed by filtration. The sodium alpha-methyl-cinnamate is then dissolved in one half to one liter of water and clarified with activated carbon and filtered.

The solution of water and sodium alpha-methyl-cinnamate is acidified with hydrochloric acid to precipitate crystals of alpha-methyl-cinnamic acid. Yields are approximately 80 %.

Starting Molecule: Benzaldehyde
Product: alpha-Methyl-cinnamic acid
Reference: (Bogert 1932)

Starting Molecule: Methoxybenzaldehyde
Product: alpha-Methyl-methoxycinnamic acid
Reference: (Woodruff 1938). See also (Bogert 1932)

Substituted alpha-Methyl-phenylacrylic Acids From Substituted Benzaldehydes

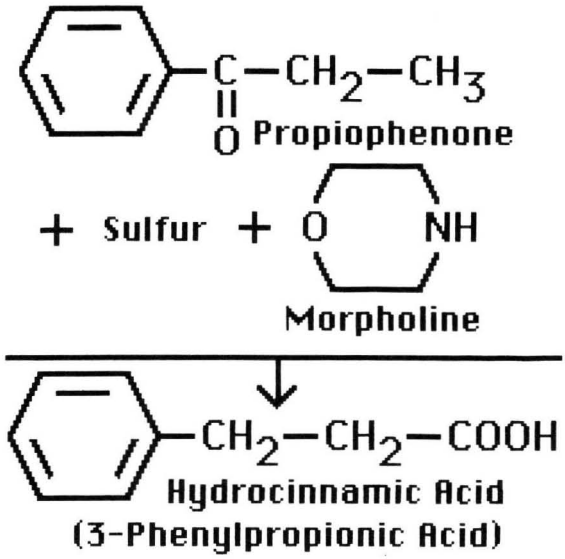


A solution is prepared containing 0.5 mole of substituted benzaldehyde, 0.5 mole of propionic anhydride and 0.5 mole of fused sodium propionate. The solution is heated (140-150 degrees) for 50 hours and then cooled. One liter of 4 molar sodium hydroxide solution is added and heated to reflux and then cooled. The cooled solution is extracted with benzene to remove the unreacted substituted benzaldehyde and stilbene. The mother liquor (the alkaline solution) is neutralized with acid and cooled, which precipitates the alpha-methyl-ß-phenylacrylic acid.

Starting Molecule: 2,5-Dimethoxybenzaldehyde
Product: alpha-Methyl-ß-2,5-dimethoxyphenylacrylic Acid
Reference: (Govindachari 1953)

Starting Molecule: 2,4,5-Trimethoxybenzaldehyde
Product: alpha-Methyl-ß-2,4,5-trimethoxyphenylacrylic Acid
Reference: (Dandiya 1962)

MODIFIED WILLGERODT REACTION
Preparation of Hydrocinnamic Acids



0.25 Mole of substituted propiophenone is mixed with 0.4 mole of sulfur, 30 mL of morpholine, refluxed for 8 hours to produce an oily substituted phenylacetothiomorpholide. The phenylacetothiomorpholide is mixed with 250 mL of 10% alcoholic sodium hydroxide and then refluxed for a total of 6 hours. An equal volume of water is added, the alcohol is evaporated. The solution is then acidified to Congo Red paper with hydrochloric acid and extracted with ether. The ether is evaporated to leave a residue of substituted hydrocinnamic acid. Yields 60 to 98 %

Starting Molecules: p-Bromoacetophenone
Reagents: Sulfur, Morpholine, Sodium Hydroxide, Ether
Product: p-Bromo-phenylacetic Acid
Reference: (Schwenk 1942)

Starting Molecules: 2,5-Dimethoxyacetophenone
Reagents: Sulfur, Morpholine, Sodium Hydroxide, Ether
Product: 2,5-Dimethoxy-phenylacetic Acid
Reference: (Schwenk 1942)

Starting Molecules: p-Methoxyacetophenone
Reagents: Sulfur, Morpholine, Water
Product: p-Methoxyphenyl Acetic Acid
Reference: (Schwenk; 1942; 1946)

Starting Molecules: p-Methoxypropiophenone
Reagents: Sulfur, Morpholine, Sodium Hydroxide, Ether
Product: p-Methoxyhydrocinnamic Acid
Reference: (Schwenk 1946)

Starting Molecules: Propiophenone
Reagents: Sulfur, Morpholine, Sodium Hydroxide, Ether
Product: Hydrocinnamic Acid
Reference: (Schwenk 1946)

Further References: (Butler 1958)

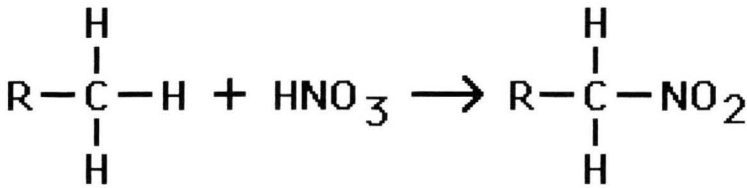
CHAPTER 19

PREPARATION OF NITROALKANES FROM ALKANES

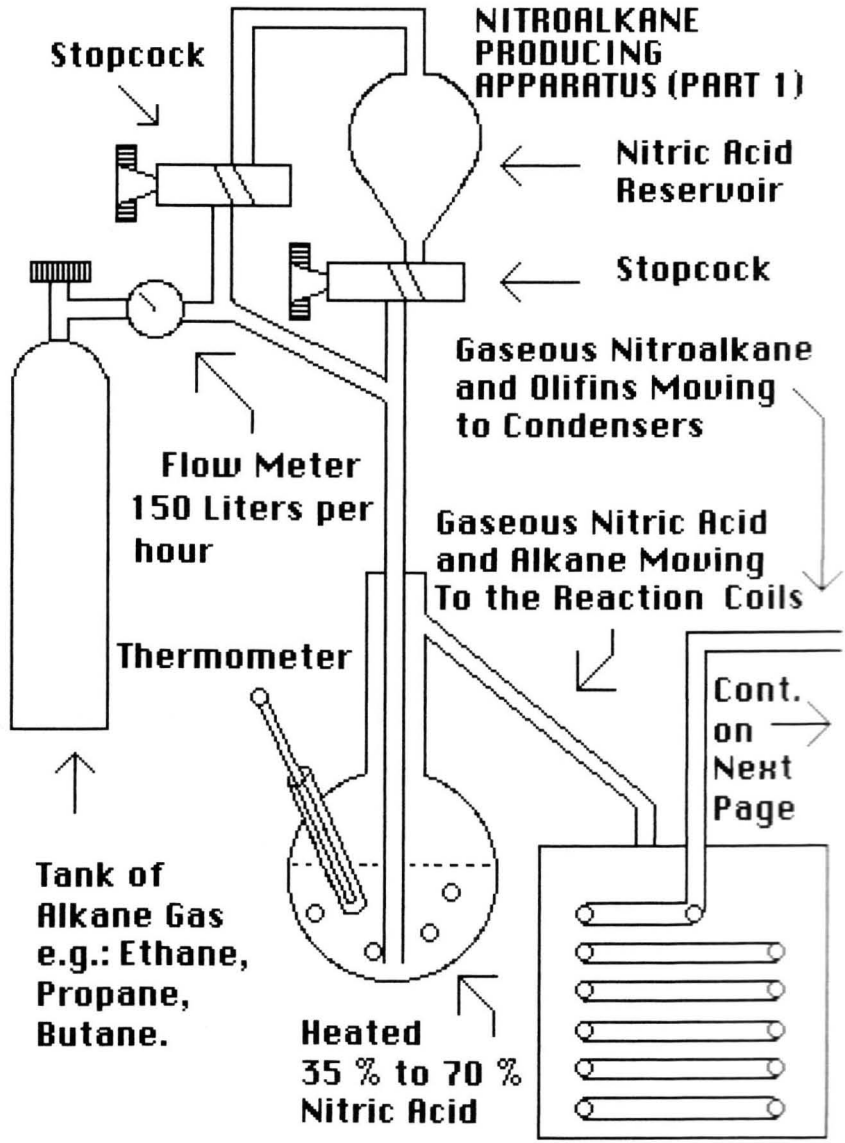
Nitroalkanes, (nitroparaffins), are used in synthetic fuels (e.g. funny car fuel and model airplane fuel) in octane boosters for automobiles, motorcycles, big rigs, in organic synthesis, solvents for lacquers and use in explosives. Nitroalkanes are generally produced by the vapor phase nitration of alkanes (paraffins).

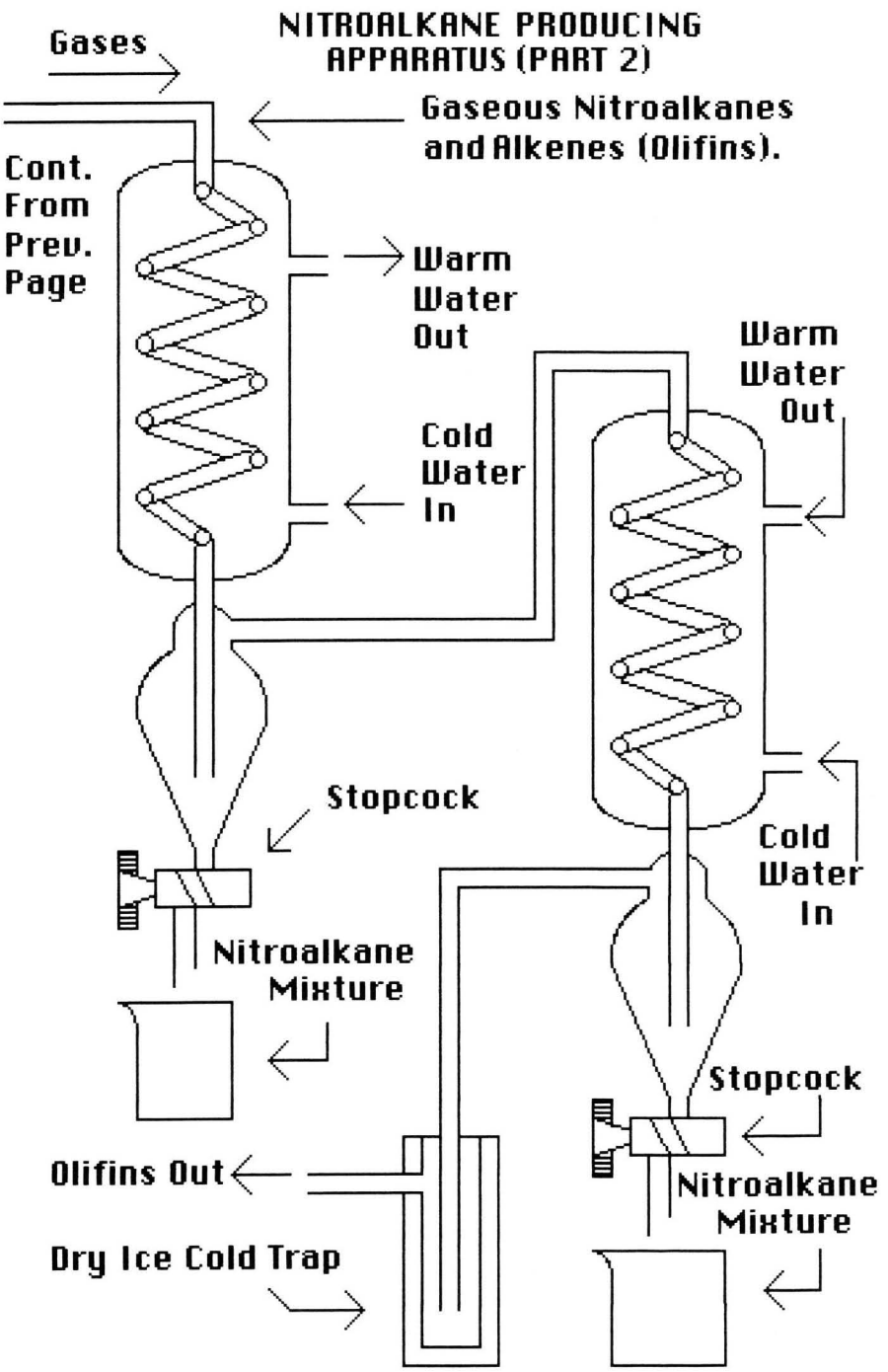
Nitromethane is explosive with difficulty. Attempts to explode nitroethane or higher homologs have been unsuccessful. No. 8 blasting caps failed to detonate nitroethane; so have attempts with red hot wire coils and burning. The vapor phase nitration has been reported to produce explosions if fuming nitric acid is used or the alkane gas is allowed to stop bubbling through the hot acid.

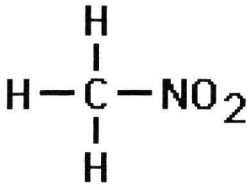
In 1872 a person by the name of Meyer first produced nitroparaffins. Little research was conducted on the preparation of nitroalkanes during the first quarter of the 1900's. In 1930 Hass, Hodge and Vanderbilt began studying the vapor phase production of nitroalkanes. The general equation is as follows:



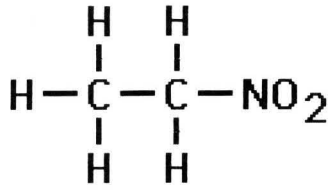
The setup and vapor phase production of nitroalkanes is not for amateurs, but maybe of interest to the readers. Check citations in the reference section.


NITROALKANE PRODUCING APPARATUS (PART 1)
Stopcock
Nitric Acid Reservoir
Stopcock
Gaseous Nitroalkane and Olifins Moving to Condensers
Flow Meter 150 Liters per hour
Gaseous Nitric Acid and Alkane Moving To the Reaction Coils
Thermometer
Cont. on Next Page
Tank of Alkane Gas e.g.: Ethane, Propane, Butane.
Heated 35 % to 70 % Nitric Acid
Reaction Coils Immersed in a heated mixture of Granular Sodium Nitrite and Potassium Nitrite


NITROALKANE PRODUCING APPARATUS (PART 2)
Gases
Gaseous Nitroalkanes and Alkenes (Olifins).
Cont. From Prev. Page
Warm Water Out
Cold Water In
Warm Water Out
Cold Water In
Stopcock
Nitroalkane Mixture
Stopcock
Nitroalkane Mixture
Olifins Out
Dry Ice Cold Trap

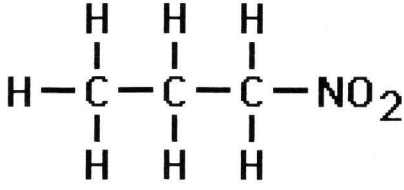


Nitromethane

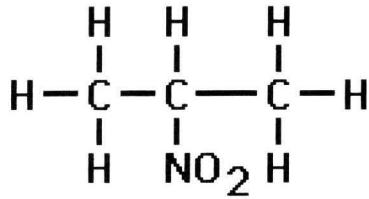


Nitroethane

The nitration of ethane produces approximately 15 % nitromethane and 85 % nitroethane.

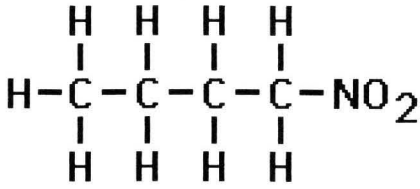


1-Nitropropane

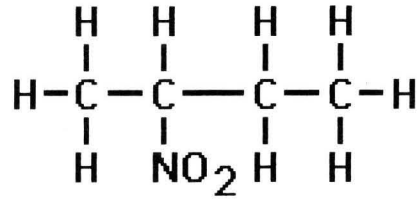


2-Nitropropane

The nitration of propane produces approximately 10 % nitromethane, 25 % nitroethane, 30 % 1-nitropropane and 30 % 2-nitropropane.



1-Nitrobutane



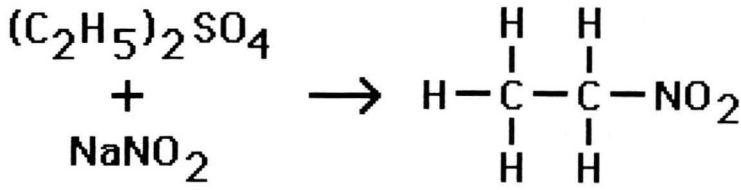
2-Nitrobutane

The nitration of butane produces approximately 5 % nitromethane, 11 % nitroethane, 5 % 1-nitropropane, 25 % 1-nitrobutane and 50 % 2-nitrobutane.

References: (Bachman 1954) (Hass 1934; 1936; 1947; 1949) (McCleary 1938) (Reidel 1956)

Preparation of Nitroethane

Nitroethane can be prepared in small quantities by the nitration of diethyl sulfate.



Nitroethane

125 Grams of diethyl sulfate, 190 grams of sodium nitrite and 240 mL of water are mixed in a separatory funnel. The funnel stopper is clamped so as not to leak and mechanically shaken for 21 hours. Occasionally the funnel is opened to release pressure and then continued to be shaken. After being mechanically shaken for 21 hours the funnel is allowed to set. Two layers form. The top layer is dried with calcium chloride or appropriate drying agent and poured into a distillation apparatus. The solution is distilled under reduced pressure (14 mm.) until the temperature reaches 60 degrees. The residue is diethyl sulfate and can be reused. The distillate is factionally distilled at atmospheric pressure. The 114-116 degree fraction is the nitroethane.

The nitroethane is washed with water, dried and redistilled at atmospheric pressure. The 114-115.5 degree fraction is collected. Nitroethane is a clear liquid that mildly smells like chloroform. Yields are approximately 50 % theoretical.

References: (McCombie 1944)

CHAPTER 20: SEPARATION OF OPTICAL ISOMERS

Dextrorotatory and Levorotatory isomers are optical isomers. A chemical composed of 50 % dextro isomer and 50 % levo isomer is called a racemic chemical.

Examples:

d-amphetamine is the dextro isomer of amphetamine.
l-amphetamine is the levo isomer of amphetamine.
d,l-amphetamine is the racemic mixture.

Dextrorotatory (Latin: dexter, right) means that the chemical rotates light to the right. Levorotatory (Latin: laevus, left) means that the chemical rotates light to the left. Racemic mixtures do not rotate light as the mixture of dextrorotatory and levorotatory neutralize the bending of the light.

The instrument that is used to determine the specific rotation to the plane of polarized light is called a polarimeter. The device is composed of a light, a tube (e.g. a small card board tube) to hold the substance being analyzed and two polarized lens (e.g. Polaroid or Nicol) at the ends of the tube, which can be turned.

The polarimeter is pointed towards the light and the lens is turned so that the maximum amount of light is being passed through the polarimeter. The substance is placed in the tube and the polarimeter is pointed towards the light again. The lens closest to the light is called the polarizer; the lens closest to the eye is called the analyzer. The analyzer lens is rotated. If the light does not dim as the lens is being rotated either clockwise or counter clockwise the substance is optically inactive. If the light dims when the analyzer lens is turned then the material is considered optically active. The degree of rotation can also be determined.

The Discovery of Optical Activity and Stereochemistry

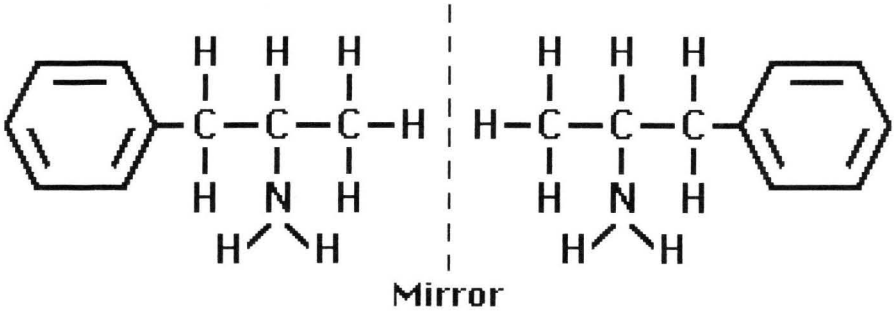
In 1815 a physicist by the name of Jean-Baptiste Biot discovered that some chemicals had optical activity. In 1848 Louis Pasteur was repeating an experiment that had been done by another scientist. Previous to this Pasteur had received his baccalaurent es

sciences by this university and was considered mediocre in chemistry. He wanted to learn more about crystallography. While crystallizing an optically inactive substance, sodium ammonium tartrate, he noticed that the some of the crystals were of different shape and carefully separated the crystals with tweezers and a magnifying glass into two piles. Then he checked them with the polarimeter.

The crystals of each pile were optically active. The original mixture was optically inactive and yet the two separate crystals were optically active (Jarowski 1943) (Pfanz 1956) (Witkop 1957). The specific rotations of each set of crystals was equal, but opposite in sign (e.g. +, -). The two piles of crystals were the same chemical, the only difference being that they rotated the plane of polarized light in opposite directions. Louis Pasteur had discovered stereochemistry.

The Stereochemistry of Amphetamine

Amphetamine exists as two isomers, the dextrorotatory and the levorotatory. They rotate the plane of polarized light in two equal, but opposite directions. They are mirror images of each other. Mirror images can be depicted on paper like this:

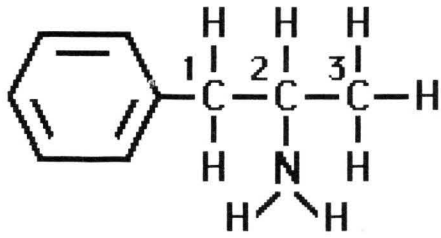


The amphetamine molecule is drawn on the left. The imaginary mirror image is then drawn on the right. In order to determine if they are isomers we try to superimpose the image on the left with the image on the right.

The rules are that we can spin the molecules around so long as we don't lift them off the paper. We can see that they are not superimposable. This means that they are isomers. Mirror images are called enantiomers.

Chirality

Molecules who's mirror images are not superimposable are called chiral molecules. The understanding of chirality helps to determine if isomers are enantiomers. This is done by finding the chiral center of the molecule. The chiral center is determined by finding a carbon atom that has four different groups of atoms attached to it.

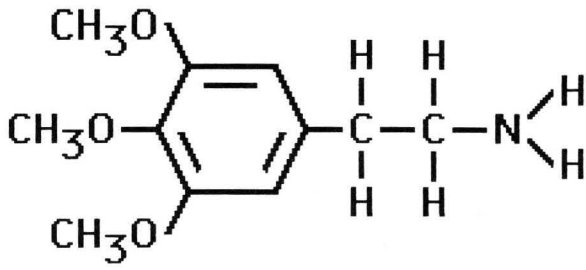


Amphetamine

Carbon 1 can not be chiral because it has two hydrogen atoms attached to it. Carbon 3 can not be the the chiral carbon because it has three hydrogen atoms attached to it. Carbon 2 is the chiral center because it has four groups (groups of atoms) attached to it that are not the same. To the right is a methyl group (CH_3). Above it is a hydrogen atom. To the left of it is a benzyl group (C_7H_7). Underneath the chiral carbon is an amino group (NH_2).

I will review:

The mirror image of the amphetamine molecule is not superimposable. The two mirror images are optical isomers called enantiomers. (If the mirror image of a molecule can be superimposed then the molecule is not an isomer). There exists a chiral center. The chiral center is carbon 2 because the four groups attached to the carbon are not the same.



Mescaline

The mescaline molecule is not chiral. Each carbon atom is attached to two of the same type of atoms.

Separation of Dextro-Phenylpropanolamine

30 Grams of d,l-phenylpropanolamine is mixed with 45 grams of d-tartaric acid and dissolved into 1350 mL of boiling alcohol. The solution is then filtered and refrigerated to precipitate 50 grams of d-phenylpropanolamine-d-bitartrate.

Evaporation of the solution leaves l-phenylpropanolamine.

The d-phenylpropanolamine-d-bitartrate can be transformed into the hydrochloride by dissolving into warm acetone, cooling in an ice bath and adding an equal molar amount of hydrochloric acid. The precipitated d-phenylpropanolamine hydrochloride is collected by suction filtration.

The resolution of racemic amphetamine can be done by the same procedure.

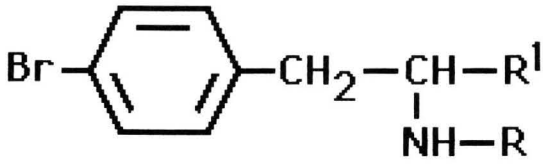
References: (Flassig 1956) (Fodor 1948) (Jatung 1931).

Starting Molecule: dl-2-Chloro-amphetamine
Product: d-2-Chloro-amphetamine tartrate
Reference: (Johns, 1938)

Starting Molecule: dl-2-Methoxy-N-methamphetamine
Product: d-2-Methoxy-N-methamphetamine tartrate
Reference: (Heizelman, 1953)

CHAPTER 21

Para-Bromination of Substituted Phenylalkylamines



Para-bromination (addition of Br to the 4 th position on the benzene ring) of substituted phenylalkylamines can activate inactive molecules or increase the potency of the parent psychoactive. It also increases the duration of action and generally produces an empathogenic effect at small to moderate dosages. This reaction will work with any phenylalkylamine which does not have a substitution on the para position.

4-Bromo Phenylalkylamine Hydrobromide Salt From Phenylalkylamine (Free Base)

Solution A:

0.6 Mole of substituted phenylalkylamine (free base) is mixed with 45 mL of glacial acetic acid.

Solution B:

4.8 Grams of bromine is added to 35 mL of glacial acetic acid.

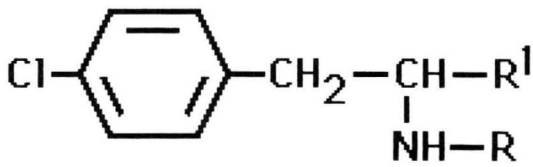
Solution B is added to solution A over a period of 15 minutes and stirred for approximately 24 hours.

Precipitation and Purification of Crude 4-Bromo-Substituted Phenylalkylamine Hydrobromide

The mixture is evaporated to leave a residue. The residue is dissolved in a minimum quantity of warm isopropyl alcohol, ether or acetone and refrigerated to precipitate the 4-bromo-substituted phenylalkylamine hydrobromide salt. The precipitated hydrobromide salt is collected by suction filtration and washed of impurities with cold ether or acetone. Yields are 50 to 60 % theoretical.

Starting Molecule: 2,5-Dimethoxyamphetamine
Product: 4-Bromo-2,5-dimethoxyamphetamine
References: (Harley-Mason 1953) (Nichols 1973; 1974) (Sepulveda 1972)

4-Para-Chlorination of Substituted Phenylalkylamine



The para-chlorination (addition of Cl to the 4 th position on the benzene ring) of substituted phenylalkylamines also increases the potency of the parent psychoactive comparable to the para-bromination.

4-Chloro-Phenylalkylamine Hydrochloride Salt From Phenylalkylamine (Free Base)

To a solution of 0.6 mole of phenylalkylamine (free base) in 65 mL glacial acetic acid, chlorine gas is bubbled until 2 grams of chlorine are absorbed. At 0 to 5 degrees is added a solution of 3.8 grams of chlorine in 65 mL of glacial acetic acid. The mixture is stirred for 6 hours and evaporated. The residue is dissolved in a minimum quantity of warm isopropyl alcohol, ether or acetone and refrigerated to precipitate the 4-chloro-phenylalkylamine hydrochloride salt which is collected by suction filtration. Yields are 40 % theoretical.

Starting Molecule: 2,5-Dimethoxyamphetamine
Product: 4-Chloro-2,5-dimethoxyamphetamine
Reference: (Nichols 1974)

CHAPTER 22

HALLUCINOGENIC DRUGS, SEROTONIN RECEPTORS, DOPAMINE AND NEUROTOXICITY

Many psychoactive (psychotropic, hallucinogenic, antidepressant) drugs have been found to bind to serotonin receptors. Amphetamine type psychoactives bind to serotonin subtype ($5\text{-}HT_2$) auto receptors (presynaptic receptors) (Battaglia 1988) (Lyon 1978). In small dosages, many of these psychoactives exhibit mood elevation effects, in larger dosages they produce hallucinations. There are many molecules which bind to this receptor in varying degrees.

Many of the amphetamine and phenylethylamine series of molecules have been found to be neurotoxic to serotonergic axions causing long term reductions in brain serotonin levels and reductions of spinal fluid 5-hydroxyindoleacetic acid (Stone 1986). Psychotropic drugs such as imipramine, amitriptyline and nortriptyline also cause reductions in 5-hydroxy-indoleacetic acid (Maas 1977). Reductions in spinal fluid 5-hydroxyindoleacetic acid have been noticed in suicide victims and violent aggression in laboratory animals (Brown 1986).

The misuse (prescribing chronically, prescribing to manic patients and/or bipolar patients) of psychostimulants has resulted in suicides, violence and severe bipolar and manic behavior.

The neurotoxicity of amphetamines has been linked to a metabolic reaction following the ingestion these molecules (Heikkila 1971). This neurotoxicity can be blocked by pre and/or post ingestion of specific serotonin reuptake inhibitor (eg. fluoxetine, etc.) before the amphetamine molecule metabolizes (approximately six hours).

Serotonin reuptake blocking molecules cause super sensitivity of the presynaptic receptors. Amitriptyline and imipramine cause super sensitivity of serotonin receptors to 5-methoxy-N,N-dimethyl-tryptamine (Friedman 1979) (De Montigany 1978). Adverse reactions in bipolar patients such as mood swings have been noted in not only with iminodibenzyl (tricyclic antidepressants) molecules (eg. nortriptyline) but also Serotonin Specific Reuptake Inhibitors (SSRI) such as fluoxetine. It is important that patients who are receiving antidepressants be monitored by the practitioner to make sure the drug is not aggravating a condition.

Imipramine blocks the neurotoxicity of p-chloroamphetamine Imipramine does not increase receptor affinities of 5-HT_2 receptors. Fluoxetine and other SSRI's (Serotonin Specific Reuptake Inhibitors) have been found to block the neurotoxicity of MDMA (Battaglia 1988a) (Sanders-Bush 1978) (Schmidt 1987) (Steranka 1978). GABA-transaminase inhibitors also block neurotoxicity (Stone 1987).

Serotonin Neurotoxins

p-Bromomethamphetamine; p-Chloroamphetamine;
p-Chloromethamphetamine; N-Hydroxy-p-chloroamphetamine
Fenfluramine; Norfenfluramine (m-trifluromethyl-amphetamine)
3,4-methylenedioxyamphetamine (MDA)
3,4-methylenedioxy-N-methylamphetamine (MDMA)
3,4-methylenedioxy-N-ethylamphetamine (MDEA)

N-Ethyl-p-chloroamphetamine, N-isopropyl-p-chloroamphetamine, and N,N-dimethyl-p-chloroamphetamine all metabolize into p-chloroamphetamine and are neurotoxic. p-Fluoroamphetamine is also neurotoxic, but depletes serotonin for a shorter time than the previously listed molecules. There is an increase in brain concentrations of 5,6-dihydroxytryptamine (endogenous neurotoxin) in rats following the administration of p-chloroamphetamine.

6-Hydroxydopamine (2,4,5-trihyroxyphenylethylamine) and 6-aminodopamine (2-amino-4,5-dihyroxyphenylethylamine) are both neurotoxic to dopamine receptors (Saner 1970) (Lundstrom 1973).

It has been speculated that superoxide and peroxide groups are responsible. If this is so. Superoxide dimutase elevation in the brain may also prevent this oxidation reaction.

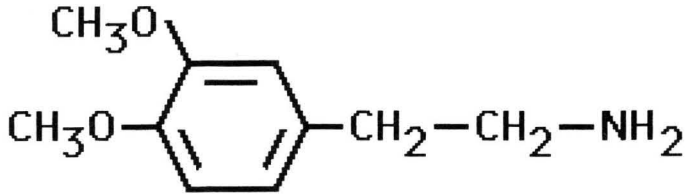
The study of phenylethylamines has lead to major breakthroughs in the understanding of brain mechanisms. The activity and mechanisms of action of these molecules are very diversified and can not be predetermined in any one theory. A simple addition of a 6-hydroxy group on the neurotransmitter, dopamine, results in a molecule which is neurotoxic. Phenylethylamine is a trace amine/neurotransmitter in the brain. By a methyl addition on to the alpha carbon results in the psychostimulant amphetamine which is neurotoxic.

The hydroxy addition on the beta carbon of methamphetamine results in the formation of norephedrine which has been found not to be neurotoxic (Smith 1974). p-Chloroephedrine has also be reported not to be neurotoxic.

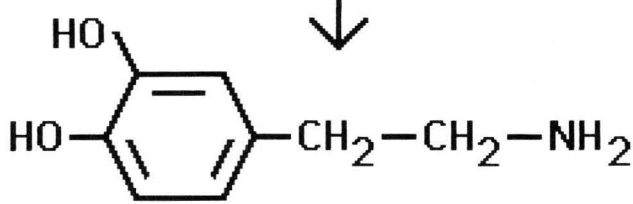
The study of phenylethylamines and related molecules begins with the building of altered structures from a parent structure (template) of known neurotransmitter molecular structures.

Preparation of Neurotransmitters & Neurotoxins

Neurotransmitters and neurotoxins can be created by the demethylation of methoxy substituted analogs.



3,4-Dimethoxyphenylethylamine



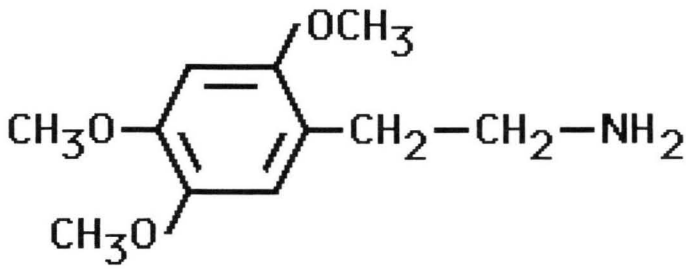
Dopamine

0.25 Mole of substituted phenylalkylamine is mixed with 180 mL of concentrated hydrochloric acid. The mixture is heated in a Carius tube for two hours at approximately 150 degrees. The darkened residue of demethylated phenylalkylamine hydrochloride is dissolved in alcohol and filtered through decolorizing carbon. Cold ether or acetone is then added to the solution to precipitate the purified demethylated phenylalkylamine hydrochloride. Yields are 75 % theoretical.

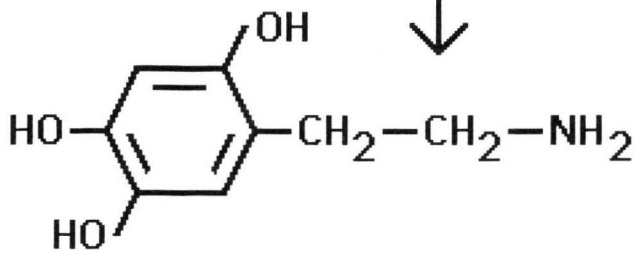
Starting Molecule: 2,5-Dimethoxyphenylethylamine
Product: 2,5-Dihydroxyphenylethylamine
Reference: (Leaf 1948)

Starting Molecule: Dimethoxyphenyl-n-propylamine
Product: Dihydroxyphenyl-n-propylamine
Reference: (Woodruff 1942)

Neurotransmitters such as dopamine (3,4-dihydroxy-phenylethylamine), adrenaline, and noradrenalin can be created using this demethylation reaction. Neurotoxins can also be created.



2,4,5-Trimethoxyphenylethylamine



2,4,5-Trihydroxyphenylethylamine

2,4,5-Trihydroxyphenylethylamine (6-hydroxy-dopamine) is created by the demethylation of 2,4,5-trimethoxy-phenylethylamine. 6-Hydroxydopamine causes decreased body weight and lack of self grooming in rats. Waxy flexibility (a catatonic-like behavior) is produced when pargyline (MAOI) is combined with these injections. Waxy flexibility is a term for a behavior when the legs or arms are moved, they remain frozen (molded) in position. This behavior is also

noted in burnt out schizophrenics and in severe forms of Parkinsonism. 6-Hydroxy-dopamine destroys dopamine neurons (Cohen 1977) (Heikkila 1971) (Lundstrom 1973). Amphetamine produces 6-hydroxydopamine in the brain. Psychiatric drugs (neuroleptics) such as chlorpromazine and thioridazine block dopamine receptors, but cause Parkinsonism with chronic use.

The neurotoxin MPP+ (1-methyl-4-phenyl pyridinium ion) causes destruction of dopamine neurons.

Neurotoxins are used in research to understand neuro mechanisms and the biochemistry of mental illness.

2,5-Dihydroxyphenylethylamine has been found to cause a disease called alcaptonuria (high urinary excretion of homogentisic acid also called 2,5-dihydroxyphenyl acetic acid) when given to rats (Leaf 1948). 2,5-Dihydroxyphenylethylamine is toxic.

Chemicals have different degrees of toxicity depending on the species in which the chemical is being tested on. MPP+ causes temporary parkinsonism in laboratory rats and then the rats will come came out of the frozen state. In humans exposed to this chemical by environmental toxins and also as a by product of the synthesis of the narcotic, MPPP, did not come out of the chemical induced parkinsonism.

There are so many enzyme and various other biochemical differences between species that scientists have to use those animals which have neurotransmitter, enzyme and metabolic similarities to humans. An example of this is the use of chickens as laboratory animals when testing the toxic effects of insecticides and nerve gasses because of the similarity of an enzyme called choline esterase. Primates are the best laboratory subjects, yet due to cost and slow reproductive rate it is not a general candidate for chemical testing.

Many of the phenylethylamines have been found to be neurotoxic. In laboratory rats and guinea pigs, the phenylethylamine neurotoxins have been found to reduce serotonin levels in their brains, which later return to normal levels so long as very large dosage of the neurotoxin have not been given. In primates, these molecules produce long term reductions in brain serotonin levels. Rats and guinea pigs metabolize dopamine and amphetamines by different metabolic routes than primates and humans (Smith 1970).

Amphetamine psychosis resembles the symptoms of schizophrenia (organo phosphate poisoning does also). para-Methoxyamphetamine has been reported to be excreted in the urine of individuals with amphetamine psychosis.

The behavioral effects of long term amphetamine abuse resemble manic-depression. Manic-depression is characterized by severe mood swings of depression and mania. Individuals who have been damaged by being prescribed amphetamine who are then diagnosed as manic-depressives are often given lithium carbonate. Lithium carbonate increases L-tryptophan reuptake and also increases 5-hydroxy indole acetic acid in the spinal fluid.

Amphetamine, methamphetamine and fenfluramine may cause aggression and violence in laboratory animals and in humans (Miczek 1989). The actions of amphetamines are much like that of cocaine and iminodibenzyl drugs. All of these drugs initially release and increase serotonin levels in the synapse; then they produce reductions of serotonin in the brain, cause super sensitivity of presynaptic serotonin receptors. All these molecules bind to cyclic AMP.

Iminodibenzyl drugs and SSRI's have been successfully used (short term) in anti-depressant therapy. Iminodibenzyl drugs and SSRI's bind to neurotransmitter transporters. This maybe the mechanism which blocks the neurotoxic action of amphetamine metabolites. SSRI's protect some neurons from endogenous neurotoxins.

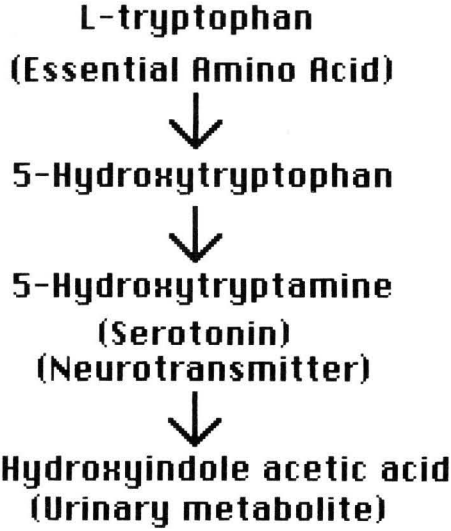
It is important that more specific drugs, with fewer toxic effects, continue to be developed. All patients should have metabolic tests done to determine which drugs will be properly metabolized. Drugs which are slowly metabolized may cause adverse reactions.

In most cases of insomnia and depression, patients are not given the opportunity to go on a trial with B-complex or L-tryptophan. L-Tryptophan is the body's own natural mood elevator and sleeping molecule (Beitman 1982) (King 1980) (Wyatt 1970). Many patients are given patent psychiatric drugs instead, which although considered being safe and effective with FDA approval, they are not a cure for either metabolic or psychological disorders.

CHAPTER 23: AN EXCITOTOXIC CAUSE OF ANXIETY

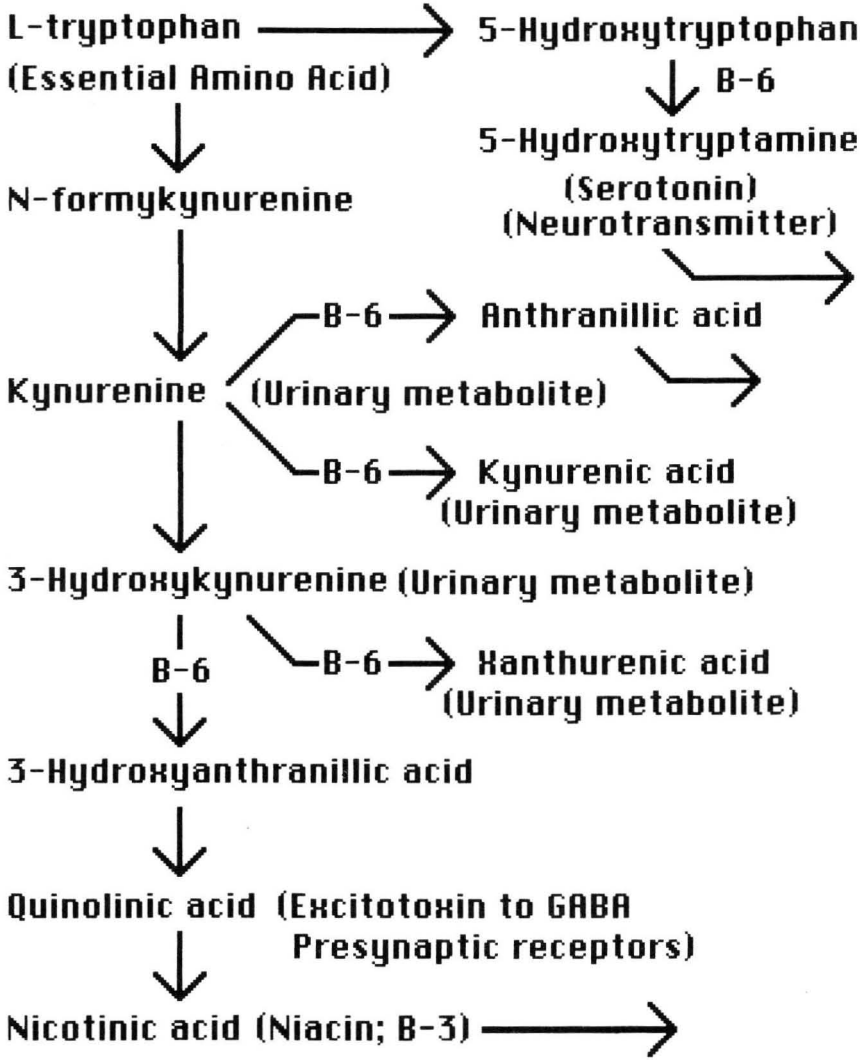
Anxiety and depression strike millions of individuals. These behavioral symptoms are primarily caused from stress. Stress burns up vitamin B and increases steroids in the body such as glucocorticoids which in turn deplete neurotransmitters in the brain. This triggers a cascade of biochemical reactions in the body and brain.

Niacin (vitamin B-3) can be made endogenously from L-tryptophan. In many cases people do not get enough L-tryptophan and or B-complex in their diets. All individuals are decedents of farm families and hunters. The diets of our lineage is that of high meat consumption which provides B-vitamins and large quantities of dairy products which contain L-tryptophan. Our modern diets, in many cases, are inadequate sources for essential nutrients of life.



L-Tryptophan is an essential amino acid. It can not be created in the body and must be obtained from natural sources or by supplement. L-Tryptophan is a precursor to a neurotransmitter called serotonin. Serotonin is necessary for sleep and balanced temperament. Laboratory studies in which rats are fed diets missing L-tryptophan, to reduce serotonin levels, develop sleep disturbances, agitation, aggression and violence. Vitamin deprivation causes endogenous biochemical reactions to take place along various pathways.

AMPHETAMINE SYNTHESES



According to the previous biochemical sequence, varying degrees of specific vitamin deprivation will cause reactions to follow specific pathways and in turn cause behavioral disturbances. Early behavioral disturbances will largely go unnoticed except to maybe the individuals experiencing them and those close to them.

Not only does inadequate consumption of nutrients cause vitamin deprivation, poor absorption of nutrients, unbalanced nutrient consumption, drugs and stress also do. The body, brain, nutrition,

environment and mind can not be separated when analyzing the causes of behavioral disturbances and mental illnesses. (Blackson 1972) (Blundell 1985) (Carney 1979, 1982) (Craig 1985) (Goggans 1984) (Hoffer 1970) (Roach 1982)

No psychiatric drugs cure mental illness. None of these drugs strengthen the body or mind. All psychiatric drugs cause biochemical imbalances (Mongilnicka 1979), vitamin deprivation (Maj 1982) (Pinto 1979, 1981), can create the symptoms of mental illness and can cause brain damage (Baldessrini 1968) (Casarino 1977) (Hudgens 1966) (Klein 1965) (O'Connell 1972).

Biochemical tests done on psychiatric patients canbe unreliable (eg. dexamethasone suppression test (Herbert)) if done improperly. Benzodiazepines interfere with the circadian rhythm of cortisol in the human body (Langer 1979). A common test called the dexamethasone suppression test has been used as an indicator of depression. Those who do not suppress the rise of cortisol after they are given a dosage of dexamethasone are labeled by some practitioners as suffering from endogenous depression. Benzodiazepines enhance dexamethasone suppression. These drugs also decrease sleep stages 3 and 4 which are necessary for the proper functioning of the brain and mind. PTSD victims with depression are super suppressors.

Those tests which give insight into biochemical abnormalities have been developed but are not being made available to psychiatric patients. Properly treating a condition involves knowing what is causing a biochemical abnormality and correcting it if necessary/possible. There will always be a need for more specific tests to determine biochemical abnormalities.

Women tend to fall prey to the psychotropic quagmire more than men. Premenstrual syndromes are caused by the hormonal fluctuations of menstrual cycles. Hormones such as progesterone cause a depletion of B-6 which in turn causes a depletion in the production of neurotransmitters such as serotonin and dopamine. Without B-6 the conversion of proteins such L-tryptophan and L-phenylalanine to neurotransmitters (e.g. serotonin, dopamine) is reduced.

Drugs (e.g. birth control pills, antidepressants, neuroleptics, antibiotics) also cause depletion of B-6. Women who are not receiving B-6 supplements are more prone to premenstrual syndromes than woman who do not take birth control pills and those woman who take B-6 supplements (Luhby 1971).

Stress increases hormones such as glucocorticoids which increase the turn over of neurotransmitters and depletes B-vitamins. Depletion of niacin swings the endogenous production of serotonin from the L-tryptophan-serotonin pathway to the L-tryptophan-quinolinic acid-niacin pathway.

Sleep disorders, nervousness, and increased startle response are a common complaints of anxiety. Quinolinic acid is an endogenous neuro-excitotoxic chemical which is formed when the L-tryptophan-serotonin pathway is switched to the L-tryptophan-quinolinic acid-niacin pathway. Quinolinic acid is neurotoxic to the GABA (gamma-amino butyric acid) presynaptic receptors (Schwarcz 1983).

GABA is a neurotransmitter that acts as a filter for incoming stimuli. Without GABA neurons our brains would be over loaded and in simple terms we would short circuit. The action and effects of benzodiazepine drugs (e.g. diazepam, flurazepam, lorazepam) are mediated by GABA neurons. The prescribing of tranquilizer drugs is a symptomatic approach to a biochemical-stress cause.

Millions of individuals, (primarily those on drugs, the elderly, and individuals of Northern European descent), can not absorb B-12 (Dawson 1984). B-vitamin deprivation causes a whole host of neurological symptoms before physical manifestations of disease become apparent. Many psychological as well as physical illnesses are caused from inborn errors in the metabolism of nutrients. Instead of treating patients with appropriate vitamins, psychotherapy and co-enzymes, patients are often prescribed drugs.

CHAPTER 24
The Brain

The brain is composed of five different types of cells. It has been estimated that the brain contains approximately 10 billion neurons (brain cells). This figure, more than likely, does not include a cell count of the cerebellum. One cell type alone, within the cerebellum called the granule, number from 10 to 100 billion.

Neurons are connected to each other by dendrites and axons like wires on a circuit board. Between each contact of the axon to the dendrite is an area called the synaptic gap. The transfer of information is carried across the synaptic gap by chemical messengers called neurotransmitters (such as adrenaline, dopamine, choline, acetylcholine, serotonin, gamma-aminobutyric acid, gamma-hydroxybutyric acid, etc.). A neuron may contain as many as 200,000 such synapses.

The synapsis is composed of receptors; presynaptic and postsynaptic receptors. The transfer of information (e.g. thoughts, emotions, behavior) is carried out by the release of neurotransmitters from the presynaptic receptors and bind to postsynaptic receptors. A very small electrical charge is transferred, by the neurotransmitter, to the next neuron, which is called neurotransmission. After neurotransmission, the neurotransmitter is then released back into the synaptic gap. The presynaptic receptor recycles this neurotransmitter back into storage sites by a mechanism called reuptake.

Neurotransmitters are not recycled indefinitely. One such enzyme which decomposes neurotransmitters, by a process known as oxidative deamination, is called monoamine oxidase (MAO). MAO metabolizes serotonin into 5-hydroxyindoleacetic acid. Monoamine oxidase is necessary because hydroxylase enzymes are capable of adding hydroxy groups, non-specifically onto neurotransmitters and trace amines transforming them into toxic neurochemicals called neurotoxins.

Another endogenous chemical, called D-glucuronic acid, detoxifies hydroxy group containing poisons, drugs and neurotoxins by forming complexes with them, which are then excreted by the body.

There are many known and unknown neurotransmitters. These neurotransmitters regulate motor and sensory functions as well as higher functions of the human brain. There are only several thousand cells in the human brain which contain neurotransmitters compared to the billions of other cells which make up the brain.

Serotonin (5-hydroxytryptamine) is a neurotransmitter that regulates diverse functions such as sleep, contentment, pain, body temperature and etc. Serotonin is produced endogenously by the decarboxylation of L-5-hydroxytryptophan. L-5-Hydroxytryptophan is produced endogenously from L-tryptophan by an enzyme called tryptophan hydroxylase. Tryptophan hydroxylase is the rate limiting enzyme in the transformation of serotonin from L-tryptophan.

It has been speculated that mental illnesses such as depression, schizophrenia, as well as insomnia, aggression and suicide are caused in part by errors in the metabolism of neurotransmitters and imbalances in these sensitive systems. Much research has been done in these areas of study over the past three decades. Several endogenous neurochemicals have been found to produce wide changes in perception and behavior.

THE RENAISSANCE OF BRAIN RESEARCH

Current problems exist in the development of new and safer drugs and nutrient therapy. Pharmaceutical firms develop drugs which they can patent. Many nutrients can not be patented and yet have been found to be effective in the treatment of many symptoms and conditions which afflict the populations. Nutrition as an alternative to toxic drugs has always had a large population of proponents.

Under current patent law naturally occurring substances are not patentable. Without patent protection and monopoly interests a drug will not be developed by pharmaceutical firms. When a firm is given money to develop a non-patentable drug, the mark up price to the public is so enormous that the cost of the drug becomes prohibitive to those who would benefit from its use. Look at the mark up on any drug. The outrageous cost of medical care and pharmaceuticals is so enormous that it is draining the life blood out of the American people.

The Quest for the Endogenous Psychotogens of Mental Illness

56 % of all individuals who are hospitalized because of mental conditions suffer from clinical B vitamin deprivation. Individuals with schizophrenic symptoms, drug addictions, alcoholism (Blackstone 1972) and depressive disorders had low levels of thiamine. Those suffering from reductions in levels of riboflavin and pyridoxine exhibited various effective illnesses (Carney 1982). Depressives suffered with low levels of pyridoxine (Carney 1979). Many newly admitted patients had multiple B-vitamin reductions.

Mania is associated with B-12 deprivation (Goggans 1984). Patients with low levels of B-12 will generally develop neurological symptoms. Malabsorption of B-12 is caused when there is a reduction of the intrinsic factor in the lower intestines. Peripheral neuropathy and abnormal mental function are also present with lack of B-12 (Roach 1982).

Parasite infestation (tape worm), gastric carcinoma, may effect intrinsic factor. Hard core vegetarians may also suffer B-12 deprivation. Age also reduces the absorption of B-12. Folic acid deficiency may cause this malabsorption. Clinical B-12 deprivation caused by the malabsorption of B-12 from protein sources may not be detected by use of the Schilling test (Dawson 1984).

Elderly patients exhibiting mental and nervous disorders have been found to be suffering with masked B-12 and folate deficiencies (Craig 1985). Yet very few are even screened. As cobamamide is the metabolically active form of B-12; its administration will cause rapid absorption and therapeutic effect.

Metabolic diseases such as the malabsorption of essential nutrients is called an orthomolecular disease. It is never cured; it can only be treated by adequate supply of the nutrient throughout the life of the individual. When the nutrient level drops the individual will exhibit the neurological symptoms prior to any physical manifestations (subclinical vitamin deprivation).

Schizophrenia has been linked (among many other factors) with an inability to have adequate production of NAD (nicotinamide adenine dinucleotide) which is B-3 co-enzyme (Hoffer 1970). Schizophrenia is also known as subclinical pellagra. Pellagra is an orthomolecular disease that slowly transforms a healthy individual into a psychotic. Some schizophrenics have responded with large dosages of vitamins. Other studies have reported that nicotinic acid was not useful. Either way it may be important that schizophrenics receive supplementation of NAD and other B-complex co-enzymes may be more effective for rapid absorption and therapeutic effect.

Transmethylation Theory of Schizophrenia

Nicotinamide is also a methyl group scavenger (Hoffer 1963). The trans-methylation theory of schizophrenia has appeared in numerous journal articles. It bases itself in the theory that over methylation of endogenous neuro-molecules transforms them into toxins and hallucinogens.

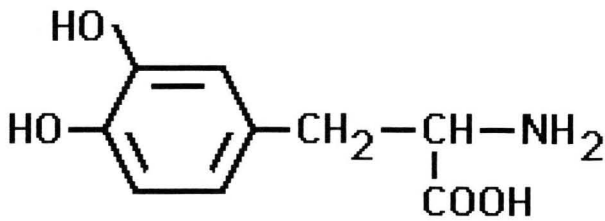
In part this theory has a basis. Schizophrenics who have been given the methyl donor methionine have shown exacerbation of the symptoms (eg. audio hallucinations). In burnt out catatonic schizophrenics, they come out of their zombie like state with methionine.

Schizophrenia is a defect involving SAM substrate. On one side is a group which is actively hallucinating (Group A) and on the other side is a group which is catatonic (Group B). Oral administration of the methyl donor, methionine, to Group B causes vocalization and short remission from the illness. In manicky schizophrenics (Group A), methionine causes exacerbation of hallucinations. When treatment is discontinued group A seems to respond to the treatment for a short remission (Cohen 1974) (Pollin 1961).

This short term recovery in Group A might indicate a super sensitivity of a receptor sight which down regulates to a more 'normal' coherent status.

Tardive Dyskinesia

Several studies have been conducted on patients who suffered with tardive dyskinesia (drug induced Parkinsonism) caused from years of taking dopamine blocking neuroleptics. The neuroleptics were discontinued which caused an increase in Parkinson symptoms.



3,4-Dihydroxyphenylalanine

L-Dopa, (l-3,4-dihydroxyphenylalanine) at a dosage of 1 gram for several weeks, the Parkinsonian syndromes increased. When the L-dopa was cut, many of the patients had recovered from tardive dyskinesia (Friedhoff 1978). This occurs because neuroleptics block

dopamine synaptic receptors causing super sensitivity of these receptors. The discontinuation of the offending molecule (neuroleptic) and use of L-dopa down regulates the receptor. The dopamine/cholinergic balance must be maintained or abnormalities in the organism will develop.

Dopamine Hypothesis of Schizophrenia

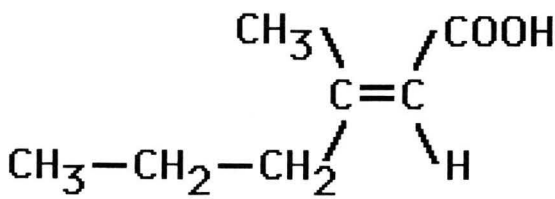
The dopamine (Meltzer 1976) hypothesis of schizophrenia is that neuroleptics block dopamine; some schizophrenics who take neuroleptics have a reduction of symptoms. Yet dopamine is a secondary factor in schizophrenia as the dopamine blocking activity of molecules does not correlate with anti-schizophrenic activity.

"The evidence for a role for dopamine in the pathophysiology of schizophrenia is compelling but not irrefutable; the "smoking gun" has not been found." (Meltzer 1976)

"Dopamine remains the neurotransmitter most likely to be involved in schizophrenia, although there is also evidence for disturbances of serotonin and norepinephrine. Post-mortem and positron emission tomographic studies suggest an increased number of D2 Dopamine receptors in some schizophrenics." (Meltzer 1987).

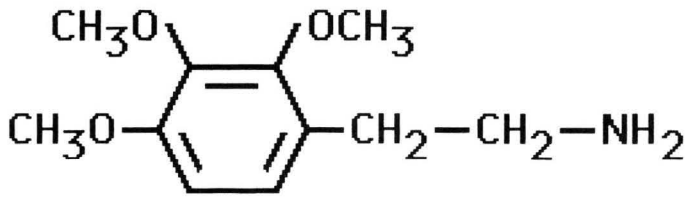
It has been speculated that the endogenous neurotoxin, 6-hydroxydopamine destroys the noradrenergic reward system in victims of schizophrenia (Stein 1971). A common soil-dwelling bacteria (25 species of Nocardia) also causes an infection which reduces brain dopamine and causes Parkinson Disease symptoms (Beaman 1990).

Schizophrenic patients sweat an odorous substance, trans-3-methyl-2-hexenoic acid, which can be identified by rats (Smith 1969); so much for psychoanalysis.



trans-3-Methyl-2-hexenoic Acid

2,3,4-Trimethoxyphenylethylamine may be a starting point from which more evidence could be gained in support of the dopamine theory.



2,3,4-Trimethoxyphenylethylamine

2,3,4-Trimethoxyphenylethylamine produces a mescaline like effect in schizophrenics, active in rats, but is inactive in normals. Mescaline has been found to be inactive or very weakly active to schizophrenics. This indicates that there maybe a defect in a specific monoamine oxidase of schizophrenics.

The case in point with the activity of 2,3,4-trimethoxyphenylethylamine in schizophrenics may be due to an endogenous MAO inhibitor or lack of specific MAO to metabolize the molecule.

2,3,4-Trimethoxyphenylethylamine would have to be taken with an MAO inhibitor to see if the combination were active in normals. A better understanding of brain biochemistry concerning this discrepancy would be of great value to the scientific and medical community.

"If measurable neurochemical changes could be related to hallucinations, delusions, and thought disorders, schizophrenia might join pellagra, neurosyphilis, and other diseases originally thought to be psychological in nature. Research on the chemistry of the brain and its regulation offers hope for understanding the causes of schizophrenia and for developing ways to treat the disorder." (Friedhoff 1988)

Currently the inactive molecule (2,3,4-timethoxyphenylethylamine) is controlled under a classification as a positional isomer of mescaline; schedule 1.

One hundred thousand new cases of schizophrenia are diagnosed each year. The millions of lives stricken with mental illness does not even touch on the magnitude of what the affliction does to families, loved ones and the very future of the country itself.

There are many biochemical theories on what could cause the symptoms of schizophrenia (Hoffer 1959) (Kety 1959). There are many psychoactive substances which are naturally occuring in the brain. Many neurotransmitter systems have yet to be studied more extensively to uncover more information on brain biochemistry and neuronal mechanisms (Budy 1961).

Schizophrenia is a smorgasbord of symptoms that are used as criteria for the diagnosis. Yet a person who is exhibiting the symptoms of this affliction may not be schizophrenic (Diehl 1989). A diagnosis of schizophrenia is usually a pigeon hole diagnosis for many non-schizophrenic diseases. Benzodiazepines, and lithium have been successfully used in the treatment of those diagnosed with schizophrenia (Donaldson 1983).

If we are to consider the possibility that mental illness is caused because of an endogenous molecule in the brain of the afflicted, we can easily draw the conclusion that drugs which block drug induced psychosis maybe useful in psychotics (Brawley 1972).

Scientists create disease models (disease paradigms) in animals to which they can then study how the disease works to develop treatments. Amphetamine has been found to increase schizophrenic symptoms in some schizophrenics. Amphetamines can also produce psychosis in normals and this action is blocked by neuroleptics (Angrist 1974). The problem is that amphetamine psychosis is not schizophrenia and neuroleptics actions are not specific except for the fact that they shut down the limbic system. Methylphenidate is more specific on dopamine receptors than on noradrenaline receptors. It has been found that methylphenidate increases schizophrenic symptoms in schizophrenics more than amphetamine does (Meltzer 1976).

Some individuals who experienced the early symptoms of schizophrenia and were given kidney dialysis; returned to normal. Victims of nerve gas and/or organo phosphorous poisoning were helped by kidney dialysis (In Cholinesterase) prior to covalent bonding (aging) of organo phosphate to choline esterase. The symptoms of organo insecticide poisoning resemble and produce depression and schizophrenia (Gershon 1961).

Schizophrenic symptoms are exacerbated in most schizophrenic individuals exposed to organo phosphates who are not currently under treatment with neuroleptics (Rowntree 1950). Pretreatment of individuals with neuroleptics prior to organo phosphate exposure blocks toxicity (In Choline and Lecithin in Brain Disorders).

A direct injection of acetyl choline given to schizophrenic subjects produced improvement is subjects (Fiamberti 1946). Several molecules which bind to muscarinic and cholinergic receptors have been found to produce short term remissions in schizophrenics (Pfeiffer 1957). Carbon dioxide has also been used to produce short term remissions in schizophrenics (Leake 1929). The ability of these molecules to affect the cholinergic receptor indicates that they may be blocking the effect of an endogenous hallucinogen which binds or is associated with a molecule which maybe a choline agonist.

There may be a common link between organo phosphate (nerve gas/insecticide) binding sights, anticholinergic binding sights of classical neuroleptics, short term remissions produced in schizophrenics by the use of cholinergics.

The aging (covalent bonding) of an unknown endogenous molecule may be directly binding to an esterase (serine) receptor sight. A pseudoesterase or other esterase maybe involved in the development of depression and also in schizophrenics. This 'theoretical schizophrenia producing molecule' maybe constantly generated in those afflicted with this condition. It may be an important strategy to block the production of this molecule than to block the neurotransmitter receptor sight that it targets. It would be interesting to see if schizophrenic patients would respond to treatment with PAM-2 (pyridine-2-aldoxime; antidote that blocks aging of organo phosphates).

Organo phosphorus molecules also cause demyelination in both peripheral nerves and spinal cord (Barnes 1951). The inhibition of pseudocholine esterase may also cause demyelination (Earl 1952). PAM-2 may also prove useful in the early treatment of MS and other diseases which result in the development of paralysis (eg. at the onset of Guillain-Barre´).

As it takes several months for choline esterase to regenerate, it may take several months of treatment to show response.

The terrorist attack with nerve gases in the Tokyo subway system and nerve gas exposure to soldiers in Desert Storm gives strength to the need for further development of drugs which inhibit the toxicity of these molecules.

Treatment of Symptoms can be Dangerous

Tricyclic antidepressants exacerbate schizophrenic symptoms. Tricyclic antidepressants such as amitriptyline are well known to cause hallucinations in non-schizophrenic individuals. Amitriptyline binds to muscarinic acetylcholine receptors (Snyder 1977).

The anticholinergic effect of amitriptyline at displacing 3-quinuclindinyl benzilate is 15 times more powerful than that of another antipsychotic medication, thioridazine which can cause delirium, hallucinations and catatonia in normal individuals.

"under the side effects: anxiety, fatigue, depression, acute hyperexcited states, tremors, hallucinations, increased muscle spasticity! I admit I don't know how to use a drug like this: what am I supposed to do if I prescribe it and the symptoms continue? Stop the drug or double the dose?" (Mendelsohn 1979)

The ability of anti-anxiety, anti-psychotics and many antidepressant drugs to induce depression, psychoses and hallucinations in non-schizophrenic patients and non-psychotic patients can be a very dangerous 'side effect' of the medication. In many cases practitioners continue to prescribe the offending medication/toxin as 'treatment' for the drug induced condition; an iatrogenic condition.

Anticholinergic delirium/syndrome is caused in individuals who are receiving powerful anticholinergic drugs, such as amitriptyline, thioridazine, clozapine, nortriptyline, doxepin, imipramine, etc. The toxic effects of these drugs resemble the psychotic reactions produced by scopolamine, atropine or the JB series of hallucinogens.

"Whatever our current concerns regarding the need for improved medications to treat schizophrenia, the overall efficacy of antipsychotic medications must be recognized as a benchmark against which newer compounds must be measured." (Schooler 1993)

"the introduction in the 1950's of antipsychotic drugs represented a landmark for psychiatry, and indeed for all of medicine. A great deal has been learned in the intervening decades about the clinical pharmacology of antipsychotic medications. Nevertheless, much still remains to be accomplished in this critical field." (Friedhoff 1988)

It has been shown that the relapse rate of schizophrenic patients is significantly reduced when patients are given moderate dosages of medications and simultaneous family psychotherapy. A low dosage medication therapy without family psychotherapy has a relapse rate of 24 % (Schooler 1993).

In a comparison of medication vs. placebo; medication was effective to a peak at 82% of the patients and placebo was effective to a peak at 35% (Keith 1993).

The most serious problem for the patient and family of the patient is that fact that there are no specific scientific tests (that are standardized) which can specifically identify a (one) biochemical cause of mental illness (Kazanetz 1979) (Reich 1975).

The scientific tests to determine biochemical abnormalities are not done on most psychiatric patients. To compound the problem of accurate determination of what medication will help the patient is that in many cases the mechanism of the drug's action is unknown (a 'primary' biochemical effect of a drug might be known, but how it causes eg. mood elevation, is not totally understood). It is unknown why some drugs work in patients and do not work in other patients.

"both research and accumulated clinical experience have demonstrated that antipsychotic drugs are not effective for all patients with schizophrenia, that effectiveness may vary with the phase of the illness, that effectiveness does not extend to all aspects of the illness, and the lack of adequate dose or patient compliance with medication taking is not the sole or even the major cause of this apparent lack of effect." (Schooler 1983)

In extensive studies done on severely depressed individuals entering a hospital. It has been found that 25 % spontaneously respond and improve without any drugs (Klerman 1965). This takes approximately one week to take place.

S-Adenosylmethionine

An endogenous enzyme substrate called S-adenosylmethionine; (SAM), has been found to have anti-depressant and anti-suicide properties when administered to depressed and suicidal patients (Agnoli 1976) (Celani 1978) (Fazio 1974). The recovery rate was 70% to 80% improvement in neurotic syndrome and 70% improvement in suicidal tendencies. A 65% improvement in hypochondriasis. I wonder what this molecule would do to obsessive compulsives? There was a 72.8 % improvement in those with a depressed mood; 81% improvement in work and other interests. This molecule is naturally occurring (Skodak 1965).

Tricyclic antidepressants decrease SAM in patients (Baldessarini 1966) (Taylor 1975).

Those factors which are considered in the recovery of those with out the use of drugs:

1) Proper diet: (which would include proper amounts of B vitamins, protein, carbohydrates etc.).
2) Protected Environment: Reduction or elimination of offending stimuli, stressors both physical (toxins) and psychological.
3) Exercise: Even minimum exercise (walking down the hallways) will be more exercise than most severely depressed individuals have had in years because of loss of will and love of life.
4) Socialization with other individuals (nurses, staff, patients, candy stripers) opens up a person from the isolation that most depressed patients usually have suffered with for years or sometimes their entire life (alone in a crowd).
5) The time factor of one week indicates that something very positive is taking place. The disease is being cured. Some conditions can take many months, years of TLC to be cured.

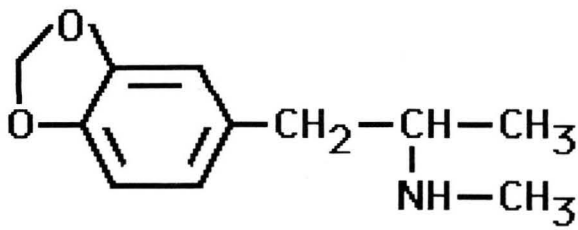
Most individuals suffering from the symptoms of mental illness are thrown back into the same toxic environment following hospital/jail release which inevitably leads to relapse.

Family counseling and social services have been shown to reduce the rate of relapse (Falloon 1982). A practitioner that is familiar with the nutritional requirements of the mentally ill is a major factor to keep the mind properly fueled.

Scientific Inquiry

Scientific inquiry follows a course of building on parent molecule to identify structural activity relationships (SAR). A psychotropic substance called MDMA was being testing in clinical settings for use as an adjunct to psychotherapy. Many proponents of this molecule found it to be particularly useful in assisting couples seeking marriage counseling and maybe useful in the treatment of PTSD. MDMA belongs to a class of molecules which are called empathogens. These molecules produce feelings of empathy and a lessening of fears in the psychotherapeutic process.

In 1986 this molecule was recommended, by those who were familiar with its uses and actions, that it be placed on schedule 3 so that further development could take place. MDMA is non-patentable as it was created in 1912. This creates a problem for all those who might have something to gain from it; pharmaceutical companies will not develop a non-patentable drug. The cost and bureaucratic nightmare to get IND (investigational new drug) and then NDA (new drug approval) is a barrier for development of any drug.

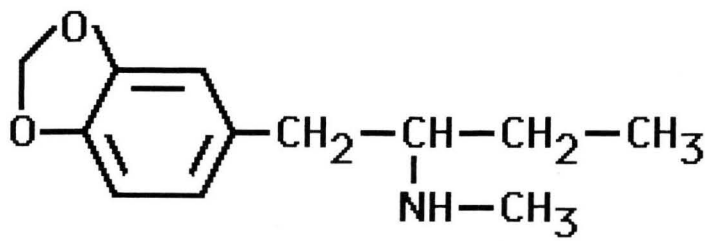


3,4-Methylenedioxy-N-methamphetamine

In 1986 the drug was place on schedule 1. Today the drug can be obtained Anywhere, USA. It is sadly ironic that those professions (law enforcement) with high rates of divorce and PTSD are authorized to arrest those in possession of this psychotropic substance.

Another class of molecules called entactogens was discovered. This family composes of a new therapeutic class of molecules. The most familiar molecule is N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine.

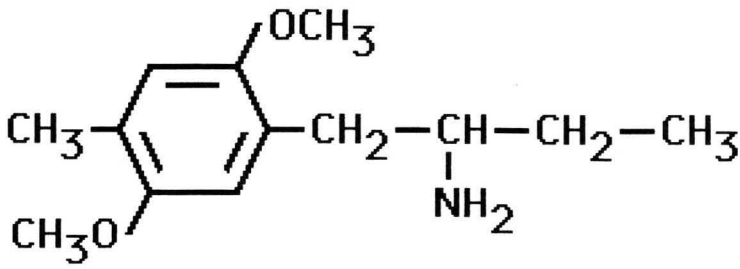
"(N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine) represents a novel type of psychoactive compound that is not hallucinogenic, but rather facilitates communication and introspective states. We propose to designate this compound as representative of a new therapeutic class to be called "entactogens". This derived from the Greek roots "en" for within or inside and "gen" to produce or originate and the Latin root "tactus" for touch. Hence, the connotation of this word is that for producing a "touching within"" (Nichols 1986).



N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine

"(N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine) instills new CNS properties termed entactogen and provides a compound devoid of hallucinogenic activity with little or no stimulant effect remaining." (Dal Cason 1990)

N-Methyl-1-(1,3-benzodioxol-5-yl)-2-butanamine is relatively easy to produce by conventional syntheses. It has not appeared as a drug of abuse.



2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane

2-Amino-1-(2,5-dimethoxy-4-methylphenyl)butane is a short acting mood elevator/anorexic (Standridge 1976) with no stimulant or hallucinogenic action (Winter 1980).

The public must have easy access to literature on scientific research and statistical analyses to determine the viability of substances for therapeutic use. Freedom of choice comes down to benefit/risk comparisons and not whether a substance or drug has been approved or not by the FDA.

Freedom of choice is our right to survival.

Anyone who has experienced or witnessed a major illness realizes the inadequacies of the medical-pharmaceutical communities and yet there are no ceilings to cost or protections for the unknowing consumer. The dilemma of drug and or medical development in this nation is much like what has happened to the automobile, electronic, steel and other industries. Simultaneously congress is being highly lobbied with money from domestic pharmaceutical and medical interests which neutralize efforts for reform of the medical-pharmaceutical system.

The Decade of the Brain has herald in a national and international renaissance of researching and understanding of the brain. The brain weighs approximately three pounds and is the most highly developed multiprocessing biological computer that has evolved on the planet. Enclosed with in it are all the happiness, joy, sadness, depression, love, laughter; everything. Composed with in it are the

creative geniuses of Thomas Jefferson, Albert Einstein, Thomas Edison, Louis Pasteur, the Wright Brothers, Charles Goodyear, Albert Hofmann, Patrick Henry, Benjamin Franklin, Linus Pauling, Alexander Shulgin, Alexander Fleming and Edward Salk to name a few. Cradled within the mind are the foundations of democracy, science, freedom, truth, justice, love, compassion, understanding, discovery, all rational thought and the ability to discover its own mechanisms.

We are the dawn of a new age. An age where scientists and researchers are deciphering the neurochemistry of the brain and unlocking the mysteries of the mind. Throughout the world neurochemists and organic chemists are being funded to continue the great exploration. Pioneers in the brain race will continue making breakthroughs as long as there is a national commitment in the development and application of new technologies. The interest and input of new minds from the private sector will guarantee that new paradigms will continue to be dynamic, visionary and progressive.

> "I know of no depository of the ultimate powers of society but the people themselves ..." Thomas Jefferson

LD-50's OF CONVENTIONAL PSYCHOATIVES

LD 50 is a term used in research which means the minimum lethal dosage of a substance in 50 out of 100 animals. Generally rats or mice are used. The following is a list of substances with their LD 50's, which appears in Psychotropic Drugs and Related Compounds (NIMH Edition) and various other sources. Least toxic are those at the top. Most toxic are at the bottom of the chart.

Drug	**LD 50 per kilogram intravenous in mice.**	**LD 50 per kilogram intravenous in rats.**
Psilocybin:	285 mg.	280 mg.
Mescaline:	157 mg.	157 mg.
Chlordiazepoxide:	95 mg.	165 mg.
Flurazepam:	84 mg.	
LSD-25:	65 mg.	16.5 mg.
Thioridazine:	51 mg.	71 mg.
Delta 9-THC:	42 mg.	29 mg.
Promethazine:	40 mg.	50 mg.
MDMA:		49 mg.
Protriptyline:	37 mg.	
Imipramine:	35 mg.	22 mg.
Nortriptyline:	28 mg.	22 mg.
Mesoridazine:	26 mg.	
Desipramine:	22 mg.	19 mg.
Amitriptyline:	21 mg.	14 mg.
Cocaine:	17.5 mg.	
Doxepin:	15-19 mg.	13-19 mg.
Chlorpramazine:	16 mg.	25 mg.
Haloperidol:	5 mg.	22 mg.
D-Methamphetamine:	9 mg.	
Nicotine:	0.3 mg.	

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